The role of a three-day trial of continuous glucose monitoring on HbA1C in noncompliant type 1 diabetic adolescents and teenagers

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2009
Dedication

This body of work is dedicated to those who have helped me most. To my parents who provided me with continued encouragement, I love and thank you. I can also never express enough sentiment to my classmates who continually worked as a team to get us all through. I wish you all the best of luck in your future careers as a PA. Last but not least, to my husband Jason, your support, patience, and time as a therapist has paid off. In merely a short time you can start buying stuff again!
Acknowledgements

I would like to express my gratitude to several people who assisted in the completion of this study. The first of these is the staff at Dr. Horner’s office. I appreciate you allowing me into your office and for your support of my pursuit of research. This is especially true in regard to my very good friend and former colleague Michelle Cleland. I cannot tell you how much I valued your insight and encouragement. And to Dr. Bork; thank you for your continued guidance focus on this project. It was a great pleasure and a privilege to work with you.
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Introduction

It is well known that diabetes carries significant risk for a multitude of microvascular and macrovascular complications and that optimizing blood sugars leads to improved health outcomes for diabetic patients. A diagnosis of type 1 diabetes carries an increased morbidity and a decreased life expectancy of between 15-27 years (Portuese & Orchard, 2005). This is especially true for patients who do not maintain good blood sugar control. Therefore, a lifelong dedication to glucose management is paramount, especially for those diagnosed at a young age. A major influence in pediatric diabetes outcome management has been the Diabetes Control and Complications Trials of 1993 and 1995. Results from these trials established that intensive insulin therapy reduced long-term micro-vascular disease such as retinopathy and nephropathy in type 1 diabetics that resulted from chronic hyperglycemia (Diabetes Control Complications Trial Research Group, 1993; The relationship of glycemic exposure," 1995). However, intensive therapy is not without risks. It can result in an increased occurrence of severe hypoglycemia that is linked to cognitive deficits in children (Gonder-Frederick, et al., 2009; Hershey, Lillie, Sadler, & White, 2004). Understandably, fear of hypoglycemia is a major barrier to intensive therapy in the pediatric population. Therefore, optimum care of pediatric type 1 diabetics should be focused on tight control of blood sugars that limits glucose excursions outside the normal range.

Intensive diabetes therapy serves to normalize hemoglobin A1c (HbA1c). Currently HbA1c is the major marker for glucose control, and main evaluator of risk of micro-vascular complications for all patients with diabetes. Out of concerns for the negative effects of hypoglycemia, the American Diabetes Association recommends using age based risk-benefit treatment guidelines. Children less than 6 years have a poor counterregulatory mechanism and hypoglycemia awareness, and therefore, have a higher HbA1c target of < 8.5 %. School aged children (6-12 years) goal level is < 8% because of low risk of hypoglycemia and complications
prior to puberty. For type 1 diabetic adolescents and young adults (13-19) the target HbA1c is < 7.5%, or three month average blood glucose of ~168mg/dl (American Diabetes, 2009). This age group is the most challenging to diabetes medical management due to developmental and psychological issues; they have higher rates of noncompliance and will be a major focus in this study.

The protocol of intensive glucose therapy includes use of a glucometer for self-monitored blood glucose (SMBG), then administration of insulin via multiple daily injections (MDI) or subcutaneous continuous infusion (SCII) with an insulin pump. A patient must complete SMBG 4-8 times daily, then accurately calculate and administer the appropriate amount of insulin in relationship to food intake. This presents significant challenges for patients. The most important of these is that it requires considerable patient cooperation and adherence to diet intake; something very difficult for adolescents and teenagers with type 1 diabetes who have variable eating and activity levels and pressure to fit in with peers. In addition, SMBG only provides snapshots of glycemic levels through the day and provides no data on nighttime values when patients are asleep. It can miss undetected hypoglycemic or hyperglycemic events that complicate glycemic control.

Current mainstay therapy also provides a challenge for practitioners in the management of glucose levels. Practitioners are limited to the SMBG values a patient presents. If the records are incomplete, treatment cannot be optimized and accurate carbohydrate to insulin levels cannot be determined. In addition, HbA1c is a valuable test for glucose evaluation, however, is merely the average blood glucose and does not reflect the degree or frequency of glucose excursions. Until recently there was no way to evaluate round-the-clock glucose measurements. The advent of continuous glucose monitoring (CGM) in diabetes care has allowed access and recording of continuous interstitial glucose data not possible with traditional SMBG. The Continuous Glucose
Monitoring System (CGMS System Gold©, Medtronic MiniMed, Northridge CA) was the first unit approved by the US Food and Drug Administration in 1999. The CGMS System Gold© is the second generation glucose monitor that measures interstitial blood glucose with a minimally invasive disposable subcutaneous enzyme tipped catheter. The system takes readings every 10 seconds and stores an average value every 5 minutes for a total of 288 daily. Data is stored into a pager sized Holter-style device that the patient wears for 72 hours. It is then downloaded via a Com-Station connector into a computer using data processing software. When completed glucose values are available in graphical and table formats for review by the healthcare team (MiniMed, 2007). See figure 1 for a sample generic representation of CGMS data.

Because the CGMS technology is novel to most, it is worth reviewing the physiology of the device. The CGMS subcutaneous catheter contains a glucose permeable membrane that is in equilibrium with interstitial glucose levels. The catheter tip is coated with the enzyme glucose oxidase. When the glucose oxidase is exposed to glucose, it creates hydrogen peroxide. The CGMS functions by detecting the current generated by the production of hydrogen peroxide (Caplin, O'Leary, Bulsara, Davis, & Jones, 2003). It records this data and calibrates it with the minimum of 4 daily SMBG readings entered by the patient. The SMBG values are used as calibration constants and assist converting the sensor signals into blood glucose values. The software for the system uses a direct linear algorithm to convert the interstitial value to blood glucose upon download. According to Medtronic Corporation, these measurements should be taken when the blood glucose levels are fairly stable and entered within five minutes of the reading to ensure proper calibration conversion (MiniMed, 2007).

There has been some reservation regarding the technology of GGSM System Gold©. The most prevalent is for accuracy, given measurement of interstitial glucose versus blood levels. Accuracy can depend on the level and degree of change of blood glucose. GCMS System Gold©
tends to over report hypoglycemia and is not very sensitive to rapid fluctuations. Maggs et al (1997) found that the concentration gradient between plasma and interstitial glucose increased when plasma glucose was lowered. This results in an artificial reporting of hypoglycemia. During rapid fluctuations (ie: post large carbohydrate load) there can be up to a 4-10 minute lag time in interstitial glucose in comparison to rate of change in plasma levels (Caplin, et al., 2003). Therefore, CGMS technology is more reliable and accurate during states of euglycemia. However, overall CGMS Gold© correlates well with frequent blood sugar measurements. In FDA trials, 98% of interstitial readings fell into the clinically acceptable range of the Consensus Error Grid (Bohme, et al., 2003; Steil, Rebrin, Mastrototaro, Bernaba, & Saad, 2003).

Additional minor drawbacks to the CGMS include user error in catheter placement, improper glucometer technique, or failure to follow SMBG entry guidelines. Therefore, the CGMS System Gold is FDA-approved only as adjunct therapy and not as a replacement to SMBG.

The implication of CGM technology is widespread to include evaluation of: recurrent asymptomatic hypoglycemia, post prandial hyperglycemia, meal and exercise effects on glucose, or when patients are unable or unwilling to complete frequent SMBG. It is particularly ideal for situations where there is discord between patient reported SMBG data and measured HbA1c. CGM technology has the potential for enhancing medical management by bringing glycemic excursions to light and improving patient-practitioner communication that can lower HbA1c. CGM technology trials have documented CGMS technology’s ability to identify glycemic excursions. A French study of 2579 type 1 diabetic children who used CGMS found that 33% of the subjects had severe unknown premeal hyperglycemia and 20% were found to have a high post meal hyperglycemia. As a result over 70% of the subject required insulin adjustments (Rosilio, et al., 1998). The question to now address is if this newly obtained information can translate into a reduction in HbA1c.
This study involved the use of the Medtronic Continuous Glucose Monitoring System Gold©. Recent studies have concluded that CGMS Gold technology has a statistically equivalent ability to intensive SMBG in reducing HbA1c in pediatric type 1 diabetics, or found no additional benefit of CGMS System Gold© guided insulin therapy that could not be achieved with SMBG (Chico, Vidal-Rios, Subira, & Novials, 2003; Deiss, Hartmann, Schmidt, & Kordonouri, 2006; Yates, Hasnat Milton, Dear, & Ambler, 2006). Therefore, one could infer because of the advantages of ease of use, and short-term compliance required, CGMS System Gold© is an excellent adjunct therapy to incomplete SMBG values in non-compliant pediatric and adolescent patients. The purpose of this study was to determine if the addition of a three-day blinded CGMS System Gold© trial on type 1 adolescent and teenage diabetics with variable SMBG compliance resulted in a reduction in HbA1c. It sought to determine if the disclosure of harmful glucose trends to both the patient and medical practitioner yields an improved glucose outcome (HbA1c). It was hypothesized that the combination of the CGMS data to incomplete SMBG records from noncompliant patients would assist ultimately in reducing HbA1c.
Methods

This study was a retrospective analysis of all applicable noncompliant type 1 diabetic patients who completed a three day CGMS Gold trial in one pediatric endocrinologist office between January 1, 2007 and December 31, 2008. The study was reviewed by the Biomedical Institutional Review Board of the University of Toledo and was approved as exempted research. Study group criteria included a HbA1c > 8%, > 6 months in the practice, age between 6 and 18 years old, a stable insulin regimen, and compliance with the 3-4 daily SMBG during CGMS trial. In order to exclude external threats to validity such as seasonal variability in HbA1C (summer vacation or holiday schedule changes), a control group was utilized. The control group was matched to the CGMS group based on age, method of insulin administration, BMI, gender, and number of years since diagnosis. These factors were selected for their potential impact on blood sugar management. With regard to age, it has been found that insulin requirements and ratios transform significantly during various stages of development (Wiegand, et al., 2008). In addition, levels of developmental maturity can play a role in compliance. The route of insulin can also affect glycemic outcomes. A meta-analytic comparison of subcutaneous continuous insulin infusion (CSII, or insulin pump) vs. multiple daily injections found that the use of CSII in type 1 DM resulted in a lower HbA1c (Jeitler, et al., 2008). In addition, overweight adolescents on intensive insulin regimens did not have any better metabolic control over normal weight peers not on intensive therapy (American Diabetes, 2009; Cakan, Ellis, Templin, Frey, & Naar-King, 2007). Therefore, a higher BMI may predispose patients to higher HbA1c levels. The remaining factors of gender and years since diagnosis were used for matching purposes only and do not have any large randomized control trial regarding specific relationship to blood sugar control.

Attempts were made to standardize care for study participants. Each patient in the study group used the same CGM System Gold© device and One-touch Ultra © blood sugar monitor
for calibration. There was only one diabetes educator who applied the device on the patients and instructed on the proper use of the instrument. Generic patterns involved insertion on Monday with specific instructions not to modify diet, exercise or sleeping schedules from normal. In addition, participants were instructed per manufacturer guidelines to input 3-4 SMBG values into the CGM for calibration. The patient returned on a Thursday where device information was downloaded into Solutions CGMS System Software 3.0 © for analysis. Results were reviewed as a team by the physician, nurse practitioner, and certified diabetes educator (CDE). The CDE called the patient with the results and insulin adjustment and instructed patients to call immediately with significant hypoglycemia or hyperglycemia. If this occurred, further adjustments were made via phone. Otherwise, the patient CGMS trial and SMBG records would be reviewed at the patient’s next follow up appointment.

The main indicator of comparison between the CGMS and control groups was HbA1c. Routine standard of care in the practice required a HbA1c be drawn on all patients every six months. For the CGMS group, the difference between pre and post CGMS HbA1c levels were obtained and compared. Next, differences between control group HbA1cs within the study window were compared to the GCM group values to determine statistical significance. Additional indicators such as the number of insulin adjustments resulting from the CGMS trial, patient appointments made during the 6-month period between HbA1c measurements, patient support system, and the reason the patient completed the CGM, were attempted but due to chart discrepancies were abandoned. Glucose excursion frequency and duration incidence were not explored as these data were inaccessible outside of use CGMS use and only available if disclosed by the patient.

For this retrospective study the following statistical hypotheses were tested. The research hypothesis proposed that follow up HbA1c levels of the CGMS group will be lower than the
control group, or $H_R = \bar{x}_{CGMS} \neq \bar{x}_{control}$. The null hypothesis proposed that there will be no statistically significant difference between the CGMS post HbA1c and control group HbA1c assuming an $\alpha=0.05$, or $H_0 = \bar{x}_{CGMS} = \bar{x}_{Control}$. 
Results

Thirty six patients in one pediatric endocrinology practice underwent a trial of the CGMS Gold between January 1, 2008 and December 31, 2008. Of these 26 met the study inclusion criteria of compliance with 3 of 4 required daily SMBG calibrations, a HbA1c > 8%, >6 months in the practice, and an age range between 6 and 18 years old. A control group of 26 patients from the same practice was developed and matched on the study demographics previously mentioned.

Data analysis was conducted using SPSS software version 16.0 © (SPSS Corporation, Chicago, IL). The CGMS and control groups were comprised of 18 females (69%) and 7 males (31%). Each group included 17 subjects (65%) who used multiple daily injections and 9 (35%) who used continuous subcutaneous infusion of insulin (CSII). However, the CGMS group and the control group differed slightly by the other variables. The youngest subject in the CGMS group was 8 and the oldest was 18 years with a mean age of 13.38 (SD ±2.82). The CGMS group also had a BMI range of 16 to 37.9 with a mean of 22.54 (SD ± 4.80). The group also varied in years since diagnosis of diabetes with a low of 1 year and a high of 13 years, with a mean of 6.77 (SD±3.18). The baseline HbA1Cs for CGM participants ranged from 8.7% to 13.3% with a mean of 10.40 (SD±1.87). However, post CGMS HbA1C values ranged from 7.7% to 13.9% with a mean of 9.91 % (SD± 2.21). This resulted in an overall change of -0.49% in HBA1c.

The youngest subject in the control group was 7 and the oldest was 18 years with a mean age of 12.42 (SD ±3.29). The control group had a BMI range of 16.4 to 25.6 with a mean of 20.86 (SD±2.51). The number of years since diagnosis ranged from 2 to 17 with a mean of 5.54 years (SD± 2.97) as a diabetic. The baseline HbA1Cs for CGM participants ranged from 6.7% to 13.7% with a mean of 9.11% (SD±1.87). Post HbA1C control group values ranged from 6.9% to 13.3% with a mean of 9.12 % (SD± 1.7). This resulted in an overall mean change of + 0.01% in HbA1c. Refer to table 1 for comparison and group data breakdown.
Further data analyses using SPSS with an independent t-test (table 2) demonstrated that the CGMS group and control group had no statistically significant difference in age, BMI, years as a diabetic or post test HbA1c. However, baseline HbA1c differed significantly (t=2.551, df=50, p=0.014). This was recognized as a problem and an analysis of covariance (ANACOVA) was used to adjust post-test HbA1C using baseline HbA1c as a covariate. This revealed no statistically significant difference in post HbA1c between the CGMS and control groups (F_{1, 45}=0.925, p=NS).
Discussion

Based upon the analysis of the data it was concluded that the application and practice of the CGMS technology in this one pediatric endocrinology practice described in the methods section of this paper did not produce a statistically significant reduction of HbA1c in noncompliant type 1 adolescent and teenage diabetics. Even though the CGMS group had a mean 0.48% reduction in HbA1c over the control group this was insufficient to reject the null hypothesis and warrant a claim for improving HbA1c. Therefore, the initial research hypothesis proposing a reduction of HbA1c in the experimental group was not supported.

From these results it could be inferred that even with a complete data set of blood sugar values, without patient compliance to diet and insulin there will be no improvement in HbA1c. Simply stated, a noncompliant patient is a noncompliant patient and any additional technological strategies to improve glycemic control are ineffective until strategies for improved motivation and support are in place. The investigator initially desired to collect data on social support, justification for CGMS trial, and appointment adherence to determine significance on compliance and HbA1c outcome but this was abandoned due to unavailability in the patient charts.

There were limitations to this investigation. First being that the study was retrospective and may lack the rigor of other approaches such as a randomized clinical trial. In this study patient attitudes toward the CGMS results were not obtainable. Ideally, future CGMS trials could be conducted in congruence and include surveys to assess patient attitude change and outcome on HbA1c. A second issue concerns the data collection of the HbA1c levels. The timing of these tests was not universal and could range anywhere within the standard 6 month window. Therefore, some patients had levels drawn 1 month after CGMS trials, whereas others had over 5 months for follow up HbA1c levels. This could have biased HbA1c levels because measurements
occurred too early or too late in relationship to the trials. Standardized timelines post CGMS trial could reduce or eliminate concern.

It is of interest that, despite the lack of statistical significance for the CGMS reduction in HbA1c, there were several patients who improved significantly. There were six patients in the CGMS group who experienced a greater than 1% reduction in HbA1c. However, there was not enough data to explain the cause of this improvement. It would be of benefit in future research to ascertain if the improvements were due to patient attitude change when confronted with data trends, optimizing medical management, chance, or a combination of all these factors. Other studies have confirmed that CGMS technology can assist in the reduction of HbA1c. However, there is no evidence-based specific guideline on how the technology can be best assist with this effort. Each study on the subject varies in design protocol, length and frequency of CGMS use (Golicki, Golicka, Groele, & Pankowska, 2008; Maggs, et al., 1997). Therefore, the data thus far has been inconclusive to support universal application. Until specific guidelines and evidence based practice are continually reproduced, CGMS technology will suffer in its effort for insurance reimbursement. This study does not support the use of CGMS technology to improve HbA1c in noncompliant adolescent and teenage type 1 diabetics.
References


The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial (1995). *Diabetes*, 44(8), 968-983.


Abstract

**Objective:** Incomplete patient blood glucose records complicate glycemic treatment plans for practitioners. This study was designed to determine if supplementation of inadequate patient obtained records with three-day Continuous Glucose Monitoring System (CGMS) System Gold© trial on noncompliant type 1 adolescent and teenage diabetics reduced HbA1c.

**Method:** 26 non-compliant type 1 diabetic subjects from one pediatric endocrinology practice underwent a trial of CGMS over 24 months. Pre and post HbA1c values were compared to a matched control group.

**Results:** The CGMS group experienced a -0.49% HbA1c reduction where the control group changed by +0.01%. However, using a ANACOVA test to correct for differences in group pre-test HbA1c revealed no statistically significant difference in post HbA1c between the CGMS and control groups (F1,45=0.925, p=NS).

**Conclusion:** Application of CGMS technology as described in this study does not produce a reduction in HbA1c in non-compliant pediatric and adolescent type 1 diabetics.
Table 1

*Group Statistics and Demographics*

<table>
<thead>
<tr>
<th></th>
<th>CGMS Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=26</td>
<td>N=26</td>
</tr>
<tr>
<td>Females</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Multiple daily injections of insulin</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Continuous Subcutaneous infusion of insulin</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>13.38 ± SD 2.81</td>
<td>12.42 ± SD 3.23</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>22.53 ± SD 4.80</td>
<td>20.85 ± 2.51</td>
</tr>
<tr>
<td>Years diabetic</td>
<td>6.77 ± SD 3.19</td>
<td>5.54 ± SD 2.99</td>
</tr>
<tr>
<td>Pre-HbA1c*</td>
<td>10.40 ± SD 1.87</td>
<td>9.11 ± SD 1.77</td>
</tr>
<tr>
<td>Post HbA1C **</td>
<td>9.91% ±SD 2.21</td>
<td>9.18 ± SD 1.70</td>
</tr>
<tr>
<td></td>
<td>N=22</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* *Sig @ p≤ 0.05*

**4 subjects did not complete post op HbA1c in the CGMS group**
Table 2

*Results of Covariance (ANACOVA)*

**Descriptive Statistics**

Dependent Variable: PostA1C

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGMS group</td>
<td>9.909</td>
<td>2.2116</td>
<td>22</td>
</tr>
<tr>
<td>Control group</td>
<td>9.188</td>
<td>1.7040</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>9.519</td>
<td>1.9651</td>
<td>48</td>
</tr>
</tbody>
</table>

**Tests of Between-Subjects Effects**

Dependent Variable: PostA1C

<table>
<thead>
<tr>
<th>Source</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>124.008 a</td>
<td>2</td>
<td>62.004</td>
<td>48.538</td>
<td>.000</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.394</td>
<td>1</td>
<td>1.394</td>
<td>1.092</td>
<td>.302</td>
</tr>
<tr>
<td>BaslineA1C</td>
<td>117.820</td>
<td>1</td>
<td>117.820</td>
<td>92.231</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td><strong>1.181</strong></td>
<td><strong>1</strong></td>
<td><strong>1.181</strong></td>
<td><strong>.925</strong></td>
<td><strong>.341</strong></td>
</tr>
<tr>
<td>Error</td>
<td>57.485</td>
<td>45</td>
<td>1.277</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4530.610</td>
<td>48</td>
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<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>181.493</td>
<td>47</td>
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<td></td>
</tr>
</tbody>
</table>

a. $R^2 = .683$ (Adjusted $R^2 = .669$)
Figure 1

3-Day CGMS Values over 24 hours

Glucose-mg/dl

Monday
Tuesday
Wednesday