Self Blood Glucose Monitoring Underestimates Hyperglycemia and Hypoglycemia as Compared to Continuous Glucose Monitoring in Type 1 and Type 2 Diabetes

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Self-Blood Glucose Monitoring Underestimates Hyperglycemia and Hypoglycemia as Compared to Continuous Glucose Monitoring in Type 1 and Type 2 Diabetes

Abstract

Objective: When glucose records from self-blood glucose monitoring (SBGM) do not reflect estimated average glucose from HgBA1, or when patients’ clinical symptoms are not explained by their SBGM records, clinical management of diabetes becomes a challenge. Our objective was to determine the magnitude of differences in glucose values reported by SBGM vs. documented by continuous glucose monitoring (CGM).

Methods: The CGM was conducted by a clinical diabetes educator/registered nurse by the clinic protocol, using the Medtronic iPRO2™ system. Patients continued SBGM and managed their diabetes without any change. Data from 4 full days were obtained and relevant clinical information was recorded. De-identified data sets were provided to the investigators.

Results: Data from 61 patients, 27 with type 1 diabetes (T1DM) and 34 with T2DM were analyzed. The lowest, highest and average glucose recorded by SBGM were compared to the corresponding values from CGM. The lowest glucose reported by SBGM was approximately 25 mg/dl higher in both T1DM (p = 0.0232) and T2DM (p = 0.0003). The highest glucose values by SBGM were approximately 30 mg/dl lower in T1DM (p = 0.0005) and 55 mg/dl lower in T2DM (p < 0.0001). HgBA1 correlated with the highest and average glucose by SBGM and CGM. The lowest glucose values were seen most frequently during sleep and before breakfast; the highest were seen during the evening and postprandially.
Conclusion: Self blood glucose monitoring estimates the average glucose accurately but underestimates glucose excursions. Continuous glucose monitoring uncovers glucose patterns that common SBGM patterns can not.
Abbreviations:
CDE = Certified Diabetes Educator; CGM = Continuous glucose monitoring; HgBA1 = Glycosylated hemoglobin; MAD = Mean absolute difference; SBGM = Self-blood glucose monitoring; T1DM = Type 1 diabetes; T2DM = Type 2 diabetes.

Introduction

Self-blood glucose monitoring (SBGM) is the foundation of intensive insulin management. Basal, nutritional and correctional insulin dosing is based on SBGM (1). In type 1 diabetes (T1DM), frequent SBGM coupled with structured insulin titration improve glycemic control (2, 3).

Type 2 diabetes (T2DM) patients who are using multiple insulin injections also benefit from SBGM (4). However, T2DM patients who do not adjust their treatment (i.e. patients on diet alone, on oral agents, or on basal or premixed insulin injection) may not necessarily show significant improvement with SBGM. Based on these observations, the current guidelines recommend adult Type 1 DM patients monitor blood glucose at least twice a day, preferentially 6-10 times a day; before meals, at bedtime, occasionally after meals, before exercise, and before critical tasks such as driving (5). Recommendations for T2DM patients are different. Those on oral hypoglycemic agents and/or basal insulin are asked to monitor blood glucose twice, at fasting and at bedtime. Patients using basal and pre-meal / pre-mixed insulin injections are guided to SBGM before meals and injections and before critical tasks (5). It is common in clinical practice that SBGM records do not correlate with patients’ symptoms or HgBA1 results. For example, patients who present with the symptoms of hypoglycemia may not have documented low blood glucose on SBGM. Alternatively, HgBA1c may be much higher than what is expected from the SBGM recordings. This can happen even in those patients who follow the SBGM guidelines and instructions. In such cases continuous glucose monitoring

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CGM can provide invaluable information (6, 7). In adult T1DM patients CGM is recommended to document hypoglycemia, and to assist correction of hyperglycemia. In T2DM, there are no guidelines (5).

The primary goal of the current study was to compare the results of SBGM and CGM in T1DM and T2DM. The hypothesis was that even four or more daily SBGM measurements will underdetect hypoglycemia as well as hyperglycemia. The secondary goal was to investigate the relationship between HgBA1 and glucose parameters determined by SBGM and CGM.

**Methods and study design**

**Study protocol:** This was a retrospective, single blinded study, where unidentified data were obtained from the CGM Clinic of the UC Davis Medical Center Endocrinology Division.

**Continuous Glucose Monitoring:** The CGM clinic is run by a Certified Diabetes Educator (CDE) who is also a Registered Nurse (RN) and a Medical Assistant. Patients with T1DM or T2DM were referred to the CGM clinic by their endocrinologists. The most common referral diagnoses were suspected hypoglycemia or hyperglycemia. Typically patients would arrive on Wednesdays. The CDE/RN inserts the Medtronic iPRO2™ CGM sensor (CGMCS) subcutaneously. After obtaining data for at least two weekdays (Wednesday through Friday) and two weekend days (Saturday, Sunday), CGM is removed on Monday. The data from the sensor are downloaded to the Medtronics –site (https://carelink.minimed.com/ipro/hcp/) for assessment of highest glucose, lowest glucose, average glucose; %-time spent with glucose values > 200 mg/dl (11.1 mmol/L), % time spent with glucose values between 70 – 200 mg/dl (3.89-11.1 mmol/L) and % time spent with glucose values <70 mg/dl (3.89 mmol/L); segmental glucose values (during sleep, before breakfast, after breakfast, before lunch, after lunch, before dinner, after dinner and evening) are determined.

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During the CGM, patients continue SBGM before meals and at bedtime and if needed at additional times using their own glucometers. They continue to manage blood glucose based on their original treatment regimen, relying on their own SBGM. Because iPRO2™ CGM does not have a display or does not provide alarm for high or low glucose, patients are blinded to the CGM results. Throughout the CGM patients keep diet records and note the time of the meals and snacks.

**Quality control measures for CGM:** The records are assessed for adequate information and optimal accuracy. Accuracy of the recordings is assessed by reviewing the CGM reports generated by the Medtronics site [https://carelink.minimed.com/ipro/hcp/](https://carelink.minimed.com/ipro/hcp/) which provides the mean absolute difference (MAD). This value expresses the average difference between the sensor and meter readings as percentage. The MAD values <28% is considered optimal (6).

Study protocol: Daily CGM recordings, each providing 288 glucose measures per 24 hours, were analyzed for four consecutive days. Data from the insertion and removal days were excluded as they were partial days and provided fewer than 288 measurements. The average MAD value (±SD) was 9.5±2.8 and no record was eliminated for having MAD > 28%. Self-blood glucose monitoring records from the same four days were also reviewed to determine the highest, the lowest and average glucose levels. The values (highest, lowest and average glucose) obtained by SBGM vs. CGM were compared. The time segments for the highest and lowest CGM-glucose were also recorded. HgbA1 results obtained within one month of the CGM measurements were used for correlations.

**Consort statement:** Seventy one records were obtained; 6 patients did not keep SBGM and diet logs; 4 patients had interruptions in the CGM records; the data from the remaining 61 patients (27 T1DM; 34 T2DM) were analyzed.

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Statistical analysis: JMP Pro 13.1 (SAS, Cary NC) was used for analysis. Normality of data was checked using the Shapiro Wilk test, and data were transformed (log, square root or cube root) if they were not normally distributed. Alternatively, non-parametric tests were used to evaluate differences, if data could not be normalized. Descriptive statistics were calculated for each variable and were reported as Mean ± Standard Deviation (SD). Within the same individual, the data obtained from SBGM and CGM were compared using paired t-tests. Data from T1DM and T2DM patients were compared using non-parametric Van der waerdan's test. Spearman correlations were calculated between HgBA1 and glucose values determined by SBGM and CGM were calculated between HgBA1 and glucose values determined by SBGM and CGM. Partial correlations were also calculated when indicated.

Results

Clinical characteristics of the study subjects (Table 1): Patients with T1DM were younger, weighed less, used less insulin and self-monitored blood glucose more frequently as compared to those with T2DM. HgBA1c levels did not differ between T1DM and T2DM patients.

Duration of time spent with hyper-, hypo- and normo-glycemia (Table 1): Continuous glucose monitoring reports the amount of time spent with glucose < 70 mg/dl (hypoglycemic); glucose between 70 – 200 mg/dl (normoglycemic); and glucose >200 mg/dl (hyperglycemic) as a percent fraction of a 24 hour day. T1DM patients spent more time in the hypoglycemic zone (84 min vs. 40 min; p = 0.009) and tended to spend less time in the normoglycemic zone (15.6 h vs. 17.6 h; p = 0.082) as compared to the T2DM patients. Percent time spent in hyperglycemic range did not differ between T1DM and T2DM (7.0 h vs. 5.7 h; p = 0.285).
Comparisons between SBGM and CGM within the same individuals (Table 2): The lowest, highest and average glucose recorded by SBGM were compared to the corresponding values obtained from CGM. In T1DM patients, the lowest glucose measured by SBGM was 28±25 mg/dl higher than that measured by CGM (p = 0.0232). Similarly, in T2DM, the lowest glucose recorded by the patient using SBGM was 25±17 mg/dl higher than that measured by CGM (p = 0.0003). In contrast, in both groups the highest glucose values documented by SBGM were lower than those obtained by CGM (in T1DM: -30±38 mg/dl; in T2DM: -55±25 (p = 0.0005 and p <0.0001, respectively). It appeared that T2DM patients tended to underestimate the highest glucose values even more so than the T1DM patients (p = 0.095). The average glucose values measured by SBGM vs. CGM were not significantly different because on the one hand SBGM overestimated the lowest blood glucose and on the other hand, SBGM underestimated the highest glucose.

Frequent time zones for hyperglycemia and hypoglycemia by CGM (Figure 1): In T1DM, 38% of the highest blood glucose values were seen after dinner and in the evening; 17% after lunch, and 15% after breakfast. In T2DM, the highest glucose values were distributed evenly to the postprandial time segments: 20% after breakfast, 18% after lunch, and 28% after dinner and in the evening.

In T1DM, the lowest blood glucose values were seen during sleep (31%) and after dinner and in the evening (29%). In T2DM, the lowest blood glucose values were seen primarily during sleep (40%) and in the evening (14%).

Correlations between HgBA1c and the other variables (Table 3): Both in T1DM and T2DM, HgBA1 correlated directly with the highest glucose and the average glucose measured by both SBGM and CGM. HgBA1 also correlated directly with the lowest glucose value recorded by

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CGM but not by SGBM. Duration of hyperglycemia (%-time with glucose > 200 mg/dl) correlated directly with HgBA1c in T2DM and showed a weaker correlation in T1DM, but this correlation disappeared when partial correlation was calculated to account for glucose. HgBA1 did not correlate with age, weight or number of SBGM testing/day in either T1DM or T2DM.

Discussion

Suspected but under-documented hypoglycemia as well as hyperglycemia is a common clinical challenge. Availability of CGM made it possible to quantitate the discrepancy between SBGM and CGM glucose values; and determine the time zones when reporting errors are most likely to occur. Glucose values by SGBM under-estimated the highest glucose values by ~30 mg/dl in T1DM, and by ~55 mg/dl in T2DM patients. Similarly, the lowest glucose values captured by SBGM were ~25 mg/dl higher than those measured by CGM in both T1DM and T2DM. The average glucose values assessed by SBGM vs. CGM were not significantly different, indicating that SBGM provided relatively accurate assessment of overall glycemia but under-estimated the excursions in daily glucose. This is an important observation because literature indicates that glucose excursions relate to vascular complications of diabetes (8, 9). In T2DM, carotid intima-media thickness (10, 11) and coronary artery stenosis (12, 13) correlate with 2-h glucose levels during oral glucose tolerance test, independent of HgBA1. Moreover, anti-diabetic agents that target postprandial glucose can regress atherosclerotic disease, independent of the changes in HgBA1c (14). Diabetic retinopathy may also relate to postprandial glucose (15).

We observed that T1DM patients spent 7h/ day and T2DM spent 5.7 h/day with glucose levels above 200 mg/dl. Hyperglycemia occurred most frequently during the evening, and after meals. These findings indicated the importance of postprandial glucose monitoring. The current recommendations are based on pre-meal glucose monitoring, in order to adjust the dose of the
short-acting insulin (5). However, patients who are on fixed insulin regimens or oral medications do not act upon this information. Moreover, by not monitoring the post-meal glucose, they do not realize the severity of their postprandial hyperglycemia. Monitoring glucose levels 1-2 hours after meals may motivate patients to modify their diet, exercise after meals, and seek medical guidance to achieve better glucose control (16-19).

On the average, T1DM patients spent 84 min/d and T2DM patients spent 40 min/d with glucose values below 70 mg/dl. The lowest blood glucose values were seen during sleep and after dinner in both T1DM and T2DM patients. Most likely explanation for the overnight hypoglycemia is over-treatment with the long-acting insulins (20). On the other hand, the evening hypoglycemia can be caused by several factors, such as inadequate food intake, late administration of insulin, correction of postprandial blood glucose with a second injection soon after food intake (“chasing”) or exercise. Management of postprandial hypoglycemia requires individual evaluation and management.

It is well established that HgBA1 correlates best with the average glucose values (21, 22). In our study the average glucose values were 172±43.2 in T1DM and 162±39 in T2DM. Calculated HgBA1 values corresponding to these average glucoses are 7.6% and 7.3%, respectively. Actual HgBa1 values of our patients were higher than these calculated values: 8.4% in T1DM and 7.9% in T2DM. The reason for the small discrepancy may be that the calculated values were based on the CGM over the recent 4 days while HgBA1 reflects the average glucose over the preceding 3 months. In addition, calculated HgBA1 does not take the duration of hyperglycemia into consideration. Our study demonstrated that %-time spent with glucose> 200 mg/dl may have some influence on HgBA1, as reported earlier by Nielsen et al. (23). Another explanation may relate to the body weight. It was previously reported that...
obesity can lower HgBA1c (20). A similar inverse correlation was reported between body weight and fructosamine as well (24).

This study had several strengths: The instructions for SBGM were provided by the RN/CDE who was independent of the study and reflected the real-life situation. Patients were blinded to the CGM data, and they did not adjust their treatments based on the CGM. Four days of SBGM and CGM data were obtained simultaneously. Both T1DM and T2DM patients were included. There were also weaknesses: Continuous glucose monitoring may have encouraged the patients to do more SBGM than they normally do, because of the three SBGMs required for calibration purposes. Hence, in daily practice, the discrepancy between CGM and SBGM may be wider.

In conclusion, this study demonstrated that CGM uncovers glucose patterns that common SBGM patterns can not; SBGM underestimates severity hyperglycemia as well as hypoglycemia. The highest CGM-glucose values are encountered during the post-prandial periods; and during the evening. The current guidelines which emphasize pre-meal SBGM miss the high glucose values occurring postprandially. Our findings make a strong case for SBGM after meals, especially in the evenings and in T2DM patients. Additional research is necessary to determine whether postprandial SBGM can improve overall glycemic control.
Acknowledgements:

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References


(ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35:1364-79.


10. **Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurttschiev T.** Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid

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Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care.* 2000;23:1830-4.


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Distribution of hypoglycemic (glucose < 70 mg/dl) and hyperglycemic (glucose > 200 mg/dl) episodes to the time zones as documented by continuous glucose monitoring in Type 1 and Type 2 diabetes patients.

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Table 1. Baseline characteristics of the study population (Mean ± SD)

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<th>Type 1 DM</th>
<th>Type 2 DM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>27 (14 F, 13 M)</td>
<td>34 (18 F, 16 M)</td>
<td></td>
</tr>
<tr>
<td><strong>Pump users (n)</strong></td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Oral agent only (n)</strong></td>
<td>0</td>
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<td></td>
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<tr>
<td><strong>Age (years)</strong></td>
<td>46.3±17.4</td>
<td>63.9±11.6</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>83.2±22.7</td>
<td>95.7±22.4</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>HgBA1c (%) (mmol/mol)</strong></td>
<td>8.4±1.2 (64±4)</td>
<td>7.9±1.0 (63±3)</td>
<td>0.130</td>
</tr>
<tr>
<td><strong>Insulin Dose/d</strong></td>
<td>31.5±20.9</td>
<td>55.8±31.4</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Frequency of SBGM/day</strong></td>
<td>4.9±1.6</td>
<td>3.9±1.0</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>CGM-% time &lt; 70 mg/dl (%) (h)</strong></td>
<td>5.8±7.1 (1.4±1.7)</td>
<td>2.8±5.8 (0.7±1.4)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>CGM-% time &gt;70 -200 (%) (h)</strong></td>
<td>65.1±17.2 (15.6±4.1)</td>
<td>73.2±19.3 (17.6±4.6)</td>
<td>0.082</td>
</tr>
<tr>
<td><strong>CGM-% time &gt;200 (%) (h)</strong></td>
<td>29.1±20.2 (7.0±4.8)</td>
<td>23.9±18.8 (5.7±4.5)</td>
<td>0.285</td>
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</tbody>
</table>

SBGM: Self Blood Glucose Monitoring;

CGM: Continuous Glucose Monitoring

Frequency of SBGM: Number of glucose measurements /day obtained by SBGM

CGM-% time: Fraction of a 24 hour day, expressed as percent ; (h): actual number of hours

P: Significance when T1DM and T2DM patients were compared using unpaired-t test.
Table 2. The lowest, highest and average glucose values recorded by SBGM and CGM in T1DM and T2DM patients

<table>
<thead>
<tr>
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<th>Type 1 DM (n= 27)</th>
<th>Type 2 DM (n= 34)</th>
<th>P&lt;sub&gt;3&lt;/sub&gt;</th>
<th>P&lt;sub&gt;2&lt;/sub&gt;</th>
<th>P&lt;sub&gt;1&lt;/sub&gt;</th>
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<tr>
<td></td>
<td>SBGM</td>
<td>CGM</td>
<td>SBGM</td>
<td>CGM</td>
<td>SBGM vs. CGM</td>
</tr>
<tr>
<td>Lowest Glucose (mg/dl)</td>
<td>106±48</td>
<td>78±37</td>
<td>28±25</td>
<td>115±36</td>
<td>90±32</td>
</tr>
<tr>
<td>Highest Glucose (mg/dl)</td>
<td>262±79</td>
<td>292±68</td>
<td>-30±38</td>
<td>209±63</td>
<td>264±50</td>
</tr>
<tr>
<td>Average Glucose (mg/dl)</td>
<td>179±49</td>
<td>172±43.2</td>
<td>6±16</td>
<td>160±41</td>
<td>162±39</td>
</tr>
</tbody>
</table>

Δ: The difference in glucose values recorded by SBGM vs. CGM

P<sub>1</sub> and P<sub>2</sub>: Significance when glucose values obtained by SBGM and CGM are compared using paired-t test within group

P<sub>3</sub>: Significance when Δ glucose values in T1DM and T2DM patients are compared to each other using unpaired t-test
Table 3. Correlations between HgBA1 and the lowest, the highest and the average glucose values recorded by SBGM vs. CGM in Type 1 and Type 2 diabetes patients; and between HgBA1 and % time spent in hypoglycemia, normoglycemia and hyperglycemia.

<table>
<thead>
<tr>
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<th>T1DM (n = 27)</th>
<th></th>
<th>T2DM (n = 34)</th>
<th></th>
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<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
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<tr>
<td>Highest Glucose</td>
<td></td>
<td></td>
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<tr>
<td>SBGM</td>
<td>0.701</td>
<td>&lt;0.0001</td>
<td>0.401</td>
<td>0.019</td>
</tr>
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<td>CGM</td>
<td>0.538</td>
<td>0.004</td>
<td>0.447</td>
<td>0.008</td>
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<tr>
<td>Lowest Glucose</td>
<td></td>
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<td></td>
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<tr>
<td>SBGM</td>
<td>0.257</td>
<td>NS</td>
<td>0.247</td>
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<tr>
<td>CGM</td>
<td>0.468</td>
<td>0.014</td>
<td>0.432</td>
<td>0.011</td>
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<tr>
<td>Average Glucose</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SBGM</td>
<td>0.621</td>
<td>0.001</td>
<td>0.405</td>
<td>0.018</td>
</tr>
<tr>
<td>CGM</td>
<td>0.649</td>
<td>0.00025</td>
<td>0.488</td>
<td>0.003</td>
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<tr>
<td>CGM % TIME GLUCOSE</td>
<td>&lt;70 mg/dl</td>
<td>-0.274</td>
<td>0.167</td>
<td>-0.281</td>
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<td>70-200 mg/dl</td>
<td>-0.293</td>
<td>0.137</td>
<td>-0.348</td>
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<tr>
<td></td>
<td>&gt; 200 mg/dl</td>
<td>0.328</td>
<td>0.095</td>
<td>0.423</td>
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</table>

r: Correlation coefficient when analyzed using Spearman correlation

p: Significance

NS: Not significant