Appendix A
Tabular Summary of Pivotal Glucose Monitoring Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objectives and design</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td><strong>Wong, et al. Diabetes Care. 2014;37:2702-2709.</strong></td>
<td>• Adults and children&lt;br&gt;• Observational study evaluated frequency of use, A1C, and complications (SH, DKA) with CGM&lt;br&gt;• Analyzed survey results from 17,317 T1D Exchange Clinic registry participants, including 4,666 adults (aged ≥26 years), 2,769 young adults (aged 18-25 years), 4,855 adolescents (aged 13-17 years), and 5,027 children &lt;13 years of age.</td>
<td>• 9% of participants reported CGM use&lt;br&gt;• CGM was associated with significantly lower A1C in children (8.3% vs. 8.6%) and adults (7.7% vs. 7.9%); no significant difference in adolescents or young adults&lt;br&gt;• Among CGM users, frequency of use ≥6 days per week was in 60% in adults, 37% young adults, 45% adolescents, and 55% children&lt;br&gt;• No significant differences in SH or DKA between CGM users and nonusers&lt;br&gt;• 41% of CGM users discontinued within 1 year</td>
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<td><strong>Battelino, et al. Diabetologia. 2012;55:3155-3162.</strong></td>
<td>• Adults and children&lt;br&gt;• Multicenter, randomized, controlled, crossover study evaluated efficacy of adding CGM to CSII in patients with T1DM&lt;br&gt;• 153 adults and children with A1C 7.5-9.5% were randomized 1:1 to CGM On/Off for 6 months, followed by crossover to other treatment arm for next 6 months (after 4-month washout); 77 patients in CGM On/Off arm vs. 76 in CGM Off/On arm&lt;br&gt;• Primary outcome was change in A1C between treatment arms&lt;br&gt;• 16-month study</td>
<td>• Mean A1C significantly was lower with CGM vs. no CGM (8.04% vs. 8.47%)&lt;br&gt;• Mean A1C reductions were significantly lower with CGM vs. no CGM for both adults and pediatric patients, with A1C changes of −0.41% and −0.46%, respectively&lt;br&gt;• After CGM discontinued, A1C levels reverted to baseline&lt;br&gt;• During CGM use, patients spent significantly less time with glucose levels &lt;70 mg/dL (3.9 mmol/L)&lt;br&gt;• No significant difference in SH incidence with CGM vs. no CGM</td>
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<td><strong>Mauras, et al. Diabetes Care. 2012;35:204-210.</strong></td>
<td>• Children only&lt;br&gt;• Randomized clinical trial evaluated CGM benefit in young children with T1DM (median duration, 3.5 years)&lt;br&gt;• 146 children aged 4-9 years with T1DM diagnosis, insulin use ≥12 months prior to study, and A1C ≥7.0% randomized to CGM or usual care&lt;br&gt;• Primary outcome was A1C decrease ≥0.5% without SH&lt;br&gt;• 26-week study</td>
<td>• 64% of patients utilized insulin pumps&lt;br&gt;• 19% of CGM and 28% of control group achieved A1C reduction of ≥0.5% without SH (not statistically significant)&lt;br&gt;• Mean change in A1C similar for CGM and control groups (−0.1 ± 0.6% for each)&lt;br&gt;• No correlation between change in A1C and frequency of CGM use&lt;br&gt;• CGM use decreased over time, with average ≥6 days/week in only 41% of CGM group at 6 months&lt;br&gt;• SH rates similarly low in both groups</td>
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*CGM was associated with A1C decrease and less time spent in hypoglycemia for both adult and pediatric patients using CSII to manage T1DM.*

*CGM provided no glycemic control benefit in young children with T1DM after 26 weeks, although parental satisfaction was high. It was postulated that limited use of CGM glucose data for T1DM management and fears of hypoglycemia might have contributed to these findings.*

*Despite evidence showing improved outcomes with CGM, relatively few patients use it, and discontinuation rates are high. Future efforts should be aimed at improving the technology to address obstacles to more widespread CGM use.*

**Although parents reported reduced concerns about hypoglycemia in their very young children with T1DM, CGM use did not translate into more aggressive management practices, and was therefore not associated with improved glycemic control.**

- Children only
- Pilot study assessed feasibility of CGM use in very young children with T1DM
- 23 children <4 years of age were enrolled
- 26-week follow-up


**Further research is needed to assess whether decreased glycemic variability and other CGM benefits have protective effects on beta-cell function that are not reflected in A1C.**

- Children only
- Randomized clinical study evaluated value of combined CSII with CGM from T1DM diagnosis for improving glycemic control and preserving beta-cell function
- 160 children aged 1-16 years with recent T1DM diagnosis (≤4 weeks prior to study entry) randomized to CSII with CGM or BGM
- Primary outcome was A1C reductions
- 12-month study


**Among adult and pediatric patients with well-controlled diabetes, CGM was more effective than BGM for decreasing A1C and reducing time spent with glucose levels out of target range.**

- Adults and children
- Multicenter, randomized clinical trial assessed efficacy and safety of CGM in patients with well-controlled T1DM
- 129 patients with intensively treated T1DM (67 aged ≥25 years, 33 aged 15-24 years, and 29 aged 8-14 years) and A1C <7.0% were randomized to either CGM (n = 67) or BGM (n = 62)
- Primary outcome was change in time per day with glucose levels ≤70 mg/dL (3.9 mmol/L)
- 26-week study

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Design</th>
<th>CGM Use</th>
<th>Primary Outcomes</th>
<th>Additional Findings</th>
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<tr>
<td>Tsalkian</td>
<td>Children &lt;4 years</td>
<td>Pilot study</td>
<td>Variable</td>
<td>Improved glycemic control</td>
<td>Limited aggressive management practices</td>
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<td>Kordonouri</td>
<td>Children 1-16 years</td>
<td>Randomized study</td>
<td>Variable</td>
<td>Improved A1C</td>
<td>Reduced glycemic variability</td>
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<tr>
<td>Beck</td>
<td>Adults and children</td>
<td>Multicenter trial</td>
<td>Variable</td>
<td>Improved A1C</td>
<td>Reduced time out of range</td>
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**Appendix:**

- T1DM managed with MDI (n = 13) or insulin pump (n = 10) at baseline
- Mean A1C not significantly changed from baseline to 6 months (7.9% vs. 8.0%)
- CGM use in month 6 was ≥6 days/week in 45%, 4-5 days/week in 10%, and <4 days/week in 45% of patients
- Frequent hyperglycemic excursions and large glucose variability detected with CGM
- 3 SH events reported in 1 patient; only 1 of these occurred during CGM use
<table>
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<tr>
<th>Authors</th>
<th>Study Details</th>
<th>Findings</th>
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</table>
| Bode, et al. for the JDRF CGM Study Group. *Diabetes Care*. 2009;32:2047-2049. | **Demonstrated sustained CGM benefits for ≥12 months in adult T1DM patients practicing intensive diabetes management, providing ability to achieve target A1C levels more safely than previously reported.** | • Adults only  
• Extension of randomized clinical study evaluating long-term effects of CGM  
• 83 adults aged ≥25 years with T1DM; 2 cohorts: 49 patients with baseline A1C ≥7.0% and 34 with baseline A1C <7.0%  
• 6-month extension of 6-month RCT  
• Multicenter, randomized clinical trial assessed efficacy and safety of CGM  
• 322 patients with T1DM (98 aged ≥25 years, 110 aged 15-24 years, and 114 aged 8-14 years) and A1C levels 7.0-10.0% were randomized to either CGM (n = 165) or BGM (n = 157)  
• Primary outcome was change in A1C  
• 26-week study  

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**T1DM managed with insulin pump (n = 75) or MDI (n = 8) at baseline**

• Median CGM frequency 6.8 days/week after 12 months

• Significant change in mean A1C at 12 months (−0.4 ± 0.6%) among patients with baseline A1C ≥7.0% vs. no significant change in subjects with baseline A1C >7.0%

• Median time per day with glucose values 71-180 mg/dL (3.94-10 mmol/L) increased significantly at 12 months; similar trend observed for both cohorts

• Incidence of severe hypoglycemia was 21.8 events per 100 person-years in first 6 months, reduced to 7.1 events in last 6 months

**At baseline, the majority of patients used insulin pump, measured glucose >5 times per day, and had mean A1C ≤8.0%**

• For patients aged ≥25 years, A1C levels decreased significantly at 26 weeks and significantly more patients achieved A1C <7.0% with CGM vs. BGM; no significant increase in hypoglycemia

• For 2 younger patient groups, no significant differences in A1C levels at 26 weeks for CGM vs. BGM

• Average CGM use ≥6 days per week for 83% of patients ≥25 years, 30% for patients 15-24 years, and 50% for patients 8-14 years of age

• SH incidence was low for both CGM and BGM patients across all 3 age groups

• Observed CGM benefits strongly associated with age, due to improved adherence in adults
CGM was helpful in detecting abnormal glucose patterns in pediatric patients with T1DM, which could in turn provide valuable input for improving diabetes management and glycemic control.

- Children only
- Observational study
- Evaluated CGM benefits for improving glycemic control and clinical decision-making in pediatric patients with T1DM
- 47 children with either (a) A1C >8.0% and T1DM management problems or (b) A1C ≤8.0% and severe/nocturnal hypoglycemia or hypoglycemia unawareness were recruited
- Evaluated A1C and number of high (>150 mg/dL [8.3 mmol/L]) and low (<70 mg/dL [3.9 mmol/L]) glucose excursions detected with CGM vs. manual logbook recording ≥4 times daily
- 6-month follow-up

- T1DM managed with MDI (n = 24) or insulin pump (n = 23) at baseline
- Mean CGM use 69.5 ± 28 hours
- High and low glucose patterns were detected at a higher rate with CGM than with logbook records among all patients (191 vs. 42), and particularly for MDI patients (120 vs. 30)
- Observed glucose patterns were used to formulate recommendations for T1DM regimen changes
- Significant A1C decrease from 8.6 ± 1.5% at baseline to 8.4 ± 1.3% at 3 months; changes sustained at 6 months

Abbreviations: A1C = glycated hemoglobin; BGM = blood glucose monitoring; CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; MDI = multiple daily injections; RCT = randomized clinical trial; SH = severe hypoglycemia; T1DM = type 1 diabetes mellitus.
**Table A2**

Glucose Monitoring in Adult Patients with T2DM (10-23)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objectives and design</th>
<th>Outcomes</th>
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| New JP, Aijan R, Pfeiffer AF, Freckmann G for the Glucose Level Awareness in Diabetes Study, *Diabet Med.* 2015;32:609-617. | • Prospective, multicenter, randomized, controlled study compared the efficacy of BGM vs. CGM with or without alarm function in maintaining euglycemia  
  • 160 patients with T1DM or T2DM, treated with MDI or CSII, were randomized to CGM without alarms (n = 48), CGM with alarms (n = 49), or BGM (n = 48)  
  • 100-day study; primary outcome was difference in time spent outside glucose target of 70-180 mg/dL (3.9-10.0 mmol/L) during days 80-100  
  • Secondary outcomes included: (1) A1C difference between arms; and (2) percentage of patients in each arm with A1C reduction ≥0.5% | • Patients in the CGM with alarms group spent significantly less time in hypoglycemia than those in the BGM group (1.0 h/day vs. 1.6 h/day; *P* = .03)  
  • Time spent outside glucose target between days 80 and 100 was not significantly different between the 3 groups  
  • For patients with T1DM, time spent outside glucose target between day 80 and 100 was significantly lower in the CGM with alarms group vs. BGM group (*P* = .015) but not significantly different for other between-group comparisons  
  • Among those treated with CSII, time spent outside glucose target was significantly different for patients in CGM without alarms vs. BGM group (−1.9 h/day; *P* = .047) and for patients in CGM with alarms vs. BGM group (−2.4 h/day; *P* = .0134)  
  • No significant difference in A1C reduction between groups (10.6% of BGM group, 27.1% of CGM without alarms group, and 24.5% of CGM with alarms group achieved A1C reductions ≥0.5%) |
  • 62 patients were randomized 3:1 to either BGM plus an intensive diabetes education/management program primarily led by diabetes nurses (n = 46) or standard counseling without BGM (n = 16)  
  • Primary endpoint was A1C change  
  • 6-month study | • At 6 months, mean A1C reduction from baseline was significantly greater in the BGM group (1.2 ± 0.1%) than in the control group (0.7 ± 0.2%) (*P* = .04)  
  • Compared with controls, significantly more BGM patients achieved target A1C <7.0% at study end (61.9% vs. 20.0%) (*P* = .005)  
  • Body weight, BMI, and waist circumference reduction were significantly greater in the BGM group vs. control group |

*Compared with BGM, CGM use with or without alarms in patients with T1DM or T2DM reduced the time spent outside glucose targets, particularly among those treated with insulin pumps.*
<table>
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<th>Reference</th>
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<tr>
<td></td>
<td>• Observational study evaluated effect of BGM on self-management behavior and metabolic outcomes in T2DM</td>
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<td>• 30 patients, including 15 in with A1C values &lt;8% (group A) and 15 with A1C ≥8% (group B), were given basic diabetes education on BGM use and interpretation, including lifestyle modification based on results</td>
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<td>• Primary endpoint was A1C</td>
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<td>• 90-day study</td>
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<td>• Structured Testing Program (STeP) study</td>
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<td>• Prospective, multicenter, cluster-randomized trial evaluated the impact of BGM on physician treatment recommendations and patient glycemic outcomes</td>
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<td>• 483 patients with poorly controlled T2DM (A1C ≥7.5%) who had never received insulin treatment were randomized to the Structured Testing Group (STG, n = 256) or the Active Control Group (ACG, n = 227). STG patients were provided with training in structured BGM and a blood glucose analysis tool, as well as quarterly physician reviews of BGM data. ACG patients were given a BG meter, but no additional tools or training and no physician reviews</td>
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<td>• STG physicians received training on interpreting BGM data and a treatment algorithm for addressing problematic BG patterns; ACG physicians received no additional training</td>
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<td>• Primary endpoint was A1C levels</td>
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<td>• 12-month study</td>
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<td>• At 90 days, A1C and mean BG values improved significantly among all patients and for group B, but no significant changes in A1C or mean BG values were observed in group A</td>
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<td>• 53% of group B patients had A1C &lt;8% at study end</td>
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<td>Study</td>
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</table>
- Patients were randomized to BGM (n = 99) or A1C-based (n = 62) intervention  
- Primary outcome was T2DM remission and regression rate; regression was defined as A1C <6%, and remission was defined as an A1C value between 6.0% and 6.4%  
- Secondary outcomes included changes in A1C and BMI and adherence to suggested lifestyle changes  
- 1-year study  
- Compared with A1C control group, a significantly higher percentage of BGM patients achieved A1C <6% (39% vs. 5%; P<.001) and A1C between 6.0% and 6.4% (37% vs. 30%; P<.01)  
- Median A1C decreased significantly more in BGM vs. control group, from 6.6% at baseline to 6.1% at 1 year (P<.05)  
- At 1 year, significantly reduced BMI values were seen in the BGM group, but not the control group (P<.001)  
- The number of BGM patients achieving lifestyle score >12 was significantly higher than A1C patients (38.4% vs. 9.7%) (P<.001) |
- 610 patients aged 40-80 years with A1C between 7% and 10% were randomized to BGM (n = 311) or non-BGM (n = 299) while receiving the oral diabetes medication gliclazide  
- Primary efficacy endpoint was between-group A1C difference  
- 27-week trial  
- A1C at 27 weeks was significantly lower in BGM vs. non-BGM patients  
- A1C in BGM group decreased from 8.12% at baseline to 6.95% at 27 weeks; in non-BGM group A1C decreased from 8.12% to 7.20%  
- Most common adverse events suggestive of mild to moderate hypoglycemia  
- Incidence of symptomatic hypoglycemia lower in BGM patients |
| O’Kane, et al. for the ESMON Study Group. *BMJ*. 2008;336:1174-1177. | In patients with a new T2DM diagnosis, BGM use was not associated with an improvement in glycemic control, and may have a negative impact on patients’ sense of well-being. | - Efficacy of Self MONitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON) study  
- Prospective, randomized controlled trial evaluated efficacy of BGM on glycemic control and psychological indices in patients with newly diagnosed T2DM  
- 184 patients aged <70 years with newly diagnosed T2DM were randomized to BGM (n = 96) or no monitoring as the control group (n = 88); both groups received core education with additional instruction provided to BGM users  
- Primary outcomes were between-group differences in A1C, psychological indices, use of oral diabetes medications, BMI, and hypoglycemic events  
- 1-year study  
- No statistically significant differences in A1C, use of oral diabetes medication, BMI, or hypoglycemia incidence were observed between BGM and control groups  
- A1C values decreased in both groups throughout the study, with mean values of 6.9% in both groups at 12 months  
- BGM group had a significantly higher score on the depression subscale of the well-being questionnaire |
<table>
<thead>
<tr>
<th>Davis, et al. for the Fremantle Diabetes Study. <em>Diabetologia</em>. 2007;50:510-515.</th>
<th>Longitudinal analysis of data from observational Fremantle Diabetes Study evaluated whether BGM improved T2DM outcomes</th>
<th>70.2% of patients used BGM at baseline</th>
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<tr>
<td><strong>BGM use was not linked to improved survival in a well-characterized community-based sample of T2DM patients.</strong> Inconsistent findings on risk of cardiac death and retinopathy among non-insulin-treated BGM users was possibly related to confounders, incomplete covariate adjustment, or chance.</td>
<td>1,280 patients who reported BGM and diabetes treatment status at Fremantle Diabetes Study entry, including a subset of 531 subjects (5-year cohort) with ≥6 annual assessments</td>
<td>38.0% of patients died during mean follow-up of 9.8 ± 3.5 years, including 15.3% of cardiac causes</td>
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<td>Outcomes included diabetes-related morbidity, cardiac death, and all-cause mortality</td>
<td>BGM use was significantly higher among patients who survived compared with those who had died at end of follow-up (73.0% vs. 65.4%)</td>
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<tr>
<td><strong>Farmer, et al. BMJ. 2007;335:132.</strong> (The DiGEM study)</td>
<td>Randomized, open, 3-arm, parallel-group study evaluated whether BGM alone or with instruction improved glycemic control in non-insulin-treated patients with T2DM</td>
<td>BGM was not independently associated with all-cause mortality, but was associated with a 79% increased risk of cardiac death and a 50% decreased risk of retinopathy among patients not treated with insulin</td>
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<tr>
<td>Study found no evidence of benefits of BGM with or without instruction on interpreting and/or incorporating results to improve self care among non-insulin-treated patients with well-controlled T2DM.</td>
<td>453 patients with T2DM and A1C ≥6.2% were randomized to BGM with advice to consult physician for help interpreting results (n = 150), BGM was provided with training on interpreting results and implementing regimen changes (n = 151), or usual self care (without BGM) as the control group (n = 152)</td>
<td>No statistically significant difference in A1C levels for 3 groups at 12 months</td>
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<td>Primary outcome was A1C level</td>
<td>At 12 months, mean A1C value was −0.14% lower for less intensive BGM group vs. controls and −0.17% lower for more intensive BGM group vs. controls</td>
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<tr>
<td>12-month study</td>
<td>Hypoglycemic episodes occurred significantly more frequently in both BGM groups compared with the non-BGM control group</td>
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<tr>
<td><strong>Karter, et al. Diabetes Care. 2006;29:1757-1763.</strong></td>
<td>Longitudinal analysis of observational data from Kaiser Permanente Northern California diabetes registry evaluated longitudinal association between BGM and glycemic control in T2DM patients</td>
<td>Increased BGM frequency in new users was associated with significant graded reduction in A1C, independent of T2DM therapy</td>
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<td>Benefits of BGM are evident in short-term for all T2DM patients initiating monitoring, but among ongoing BGM users, benefits of monitoring only demonstrated for patients receiving pharmacologic treatment.</td>
<td>16,091 patients initiating BGM (new-user cohort) and 15,347 ongoing BGM users (prevalent-user cohort)</td>
<td>For pharmacologically treated prevalent BGM users only, changes in BGM frequency showed a significant inverse relationship with A1C changes</td>
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<tr>
<td>Assessments based on pharmacy use (number of blood glucose test strips dispensed) and A1C testing</td>
<td>4-year study</td>
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</table>
• Evaluated relationship between BGM and T2DM-related morbidity and all-cause mortality  
• 3,268 patients with T2DM were allocated to BGM or non-BGM group depending on whether monitoring was documented for ≥1 year during observation period and prior to non-fatal endpoint  
• Endpoints included diabetes-related morbidity (non-fatal MI, stroke, foot amputation, blindness, or hemodialysis) and all-cause mortality  
• BGM group had significantly higher fasting blood glucose and A1C levels at baseline and throughout observation period  
• After a mean follow-up of 6.5 ± 1.6 years, 45.3% of patients initiated BGM prior to reaching a study endpoint  
• Incidence of nonfatal endpoints was significantly lower for BGM vs. non-BGM group (7.2% vs. 10.4%); this was primarily due to decreased risk of macrovascular endpoints (e.g., MI, stroke)  
• Of the 3.7% of patients who died, a significantly higher proportion were in the non-BGM group (4.6% vs. 2.7%)  
• After adjusting for confounders, BGM was associated with a statistically significant 51% decrease in mortality and a 32% reduction in combined nonfatal endpoints, despite an increased risk of microvascular events |
| --- | --- | --- |
| Davidson, et al. *Am J Med*. 2005;118:422-425. (Sometimes referred to as the King-Drew Medical Center Study) | **Randomized, single-blind clinical trial evaluated changes in A1C levels with pre-and postprandial glucose testing among patients with T2DM who were not receiving insulin** | • 88 patients were randomized to BGM (n = 43), with preprandial and postprandial glucose testing conducted 6 days/week, or control (n = 45)  
• 6-month study  
• No significant difference in A1C at 6 months between BGM and control groups, although patients in both groups had significant A1C reductions at study completion |
| Franciosi, et al. for the QuED Study Group. *Diabet Med*. 2005;22:900-906. | **Prospective, longitudinal study evaluated the impact of BGM use and frequency on metabolic control in non-insulin-treated T2DM patients** | • 1,896 patients were recruited from outpatient diabetes clinics and asked to complete BGM questionnaires every 6 months  
• Outcome was impact of BGM on A1C  
• 3-year study  
• 22% of patients were treated with diet alone, with 78% receiving oral medication  
• 41% of patients used BGM ≥1 time weekly  
• No significant relationship between BGM use or frequency and A1C value  
• BGM use was not a predictor of improved metabolic control for any of the subgroups analyzed |

*BGM use is a marker of improved clinical outcomes among patients with T2DM, with evidence that BGM use is associated with decreased diabetes-related morbidity and all-cause mortality.*
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<td>(Sometimes referred to as the German-Austrian study)</td>
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<tr>
<td><strong>Meal-related BGM in combination with an eating diary and a structured counseling program improved glycemic control in non-insulin-treated T2DM patients.</strong></td>
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- Prospective, multicenter, randomized, controlled clinical study evaluated effect of meal-related BGM on glycemic control and well-being in non-insulin-treated T2DM patients.
- 250 patients with A1C values between 7.5% and 10% who were undergoing T2DM therapy consisting of diet alone or diet plus sulfonylureas or metformin were randomized to either BGM use (n = 113 in per protocol analysis) with standardized counseling and instruction to maintain a diary on blood glucose values and meals, or a control group (n = 110 in per protocol analysis) which received non-standardized counseling on diet and lifestyle.
- Primary endpoint was A1C change.
- 6-month study.

- In per-protocol analysis, BGM patients had significantly lower A1C levels at 24 weeks compared with control patients, with reductions of 1.0 ± 1.08% vs. 0.54 ± 1.41%, respectively.
- BGM patients experienced significant improvements in the depression and lack of well-being subscales on a general well-being assessment.
- During 6-month follow-up, 87% of BGM patients continued with monitoring and metabolic status remained stable.

Abbreviations: A1C = glycated hemoglobin; ACG = active control group; BG = blood glucose; BGM = blood glucose monitoring; BMI = body mass index; MI = myocardial infarction; STG = structured testing group; T2DM = type 2 diabetes mellitus; WHO = World Health Organization.
Table A3
BGM and CGM in Patients with Pregnancy Complicated By Diabetes (24-30)

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<thead>
<tr>
<th>Reference</th>
<th>Objectives and design</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Yu, et al. <em>J Clin Endocrinol Metab.</em> 2014;99:4674-4682.</td>
<td>• Clinical study evaluated effectiveness of CGM for glycemic control and pregnancy outcomes in patients with GDM</td>
<td>• After week 5 of the study, SDBG, MAGE, and MODD were significantly lower in the CGM group compared with the routine care group</td>
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<td>Supplementary CGM combined with routine antenatal care improved glycemic control and pregnancy outcomes in patients with GDM.</td>
<td>• 340 pregnant women with GDM at 24 to 28 weeks’ gestation were allocated to either intermittent CGM (n = 150) or routine care (n = 190); patients also performed 7 daily BGM measurements</td>
<td>• CGM patients had a significantly lower risk of preeclampsia and primary cesarean delivery vs. patients in the routine care group</td>
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<td>• Maternal outcomes included mean blood glucose, SDBG, MAGE, MODD (defined as mean of absolute value of difference between glucose measurements on 2 consecutive days), preeclampsia, and cesarean delivery. Neonatal outcomes included premature delivery (&lt;37 weeks), birth weight, and neonatal hypoglycemia.</td>
<td>• Infants born to CGM patients had a significantly lower birth weight and a significantly reduced risk of macrosomia, hypoglycemia, or premature delivery compared with infants of routine care patients</td>
</tr>
<tr>
<td>Secher, et al. <em>Diabetes Care.</em> 2013;36:1877-1883.</td>
<td>• Randomized trial evaluated whether intermittent real-time CGM improved glycemic control and pregnancy outcomes in women with pregestational diabetes</td>
<td>• CGM and non-CGM patients had similar A1C levels, plasma glucose values and hypo-and hyperglycemia profiles, and a comparable risk of severe hypoglycemia throughout their pregnancies</td>
</tr>
<tr>
<td>Intermittent use of real-time CGM during pregnancy in addition to daily BGM did not improve glycemic control or pregnancy outcomes in an unselected population of women with pre-gestational diabetes who performed BGM daily.</td>
<td>• 123 women with T1DM and 31 with T2DM were randomized to either routine care plus real-time CGM for 6 days at 8, 12, 21, 27, and 33 weeks gestation (n = 79) or routine care alone (n = 75); patients also performed 7 daily BGM measurements</td>
<td>• Prevalence of large-for-gestational-age infants was not significantly different between the CGM and non-CGM group (45% vs. 34%)</td>
</tr>
<tr>
<td>Murphy, et al. <em>BMJ.</em> 2008;337:a1680.</td>
<td>• Study evaluated effectiveness of CGM (unmasked) for improving glycemic control, infant birth weight, and risk of macrosomia in pregnant women with T1DM and T2DM</td>
<td>• No statistically significant differences in A1C levels were observed between the 2 groups at study entry or throughout the first 2 trimesters</td>
</tr>
<tr>
<td>CGM during pregnancy was associated with improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia.</td>
<td>• Prospective, open-label, randomized controlled trial</td>
<td>• CGM patients had lower mean A1C levels from 32 to 36 weeks’ gestation compared with non-CGM patients (5.8 ± 0.6% vs. 6.4 ± 0.7%)</td>
</tr>
<tr>
<td></td>
<td>• 71 patients with either T1DM (n = 46) or T2DM (n = 25) were enrolled and randomized to either antenatal care plus intermittent CGM (n = 38) or standard antenatal care (n = 33) throughout their pregnancy; patients also performed ≥4 BGM measurements daily</td>
<td>• Infants born to CGM patients had lower birth weight and a reduced risk of macrosomia compared with infants of patients in the control arm</td>
</tr>
<tr>
<td></td>
<td>• Primary outcome was A1C values assessed during second and third trimester of pregnancy</td>
<td></td>
</tr>
</tbody>
</table>
| McLachlan, et al. *Aust NZ J Obstet Gynaecol.* 2007;47:186-190. | • CGM is well tolerated and clinically useful in the management of GDM and preexisting diabetes in pregnancy. CGM provided additional information that was not evident from traditional BGM. | • Study evaluated CGM for usefulness, patient tolerability, accuracy, and value as a tool for medical decision-making in pregnant women with diabetes.  
• 55 pregnant women with diabetes, including 37 with GDM, 10 with T2DM, and 8 with T1DM, were monitored with CGM at key times throughout their pregnancy; patients also performed ≥4 BGM measurements daily.  
• 62% of CGM reports provided additional information leading to treatment regimen changes, including detection of postprandial hyperglycemia and overnight hyper- and hypoglycemia.  
• 77% of participants reported that CGM benefits outweighed any inconvenience associated with monitoring. |
| --- | --- | --- |
| Chen, et al. *J Matern Fetal Neonatal Med.* 2003;14:256-260. | • CGM is helpful for monitoring women with GDM and can accurately detect high postprandial blood glucose levels and nocturnal hypoglycemic events that may go unrecognized by intermittent BGM. | • Prospective pilot study comparing daily glycemic profile with CGM vs. BGM in women with GDM.  
• 57 women with GDM, including 47 consecutive patients from an Israeli clinic and 10 from a US clinic, were recruited; patients used CGM over a 72-hour period while also performing BGM 6 to 8 times per day using the fingerstick method.  
• 3-day study.  
• Israeli group (24 treated with insulin plus diet, 23 with diet alone): mean time with undetected hyperglycemia (>140 mg/dL [7.8 mmol/L]) based on BGM was 132 ± 31 min/day among insulin-treated patients and 94 ± 23 min/day in patients treated with diet alone; 14 patients (all insulin-treated) had nocturnal hypoglycemic events (<50 mg/dL [2.8 mmol/L]) detected via CGM.  
• American group (all 10 treated with insulin): mean time with undetected hyperglycemia based on BGM was 78 ± 13 min/day; 8 patients had nocturnal hypoglycemic events detected via CGM.  
• All insulin-treated patients had dosage changes based on CGM data. |
| de Veciana, et al. *N Engl J Med.* 1995;333:1237-1241. | • Adjustment of insulin therapy based on postprandial rather than preprandial blood glucose values in patients with GDM improves glycemic control and decreases the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery. | • Randomized study compared the efficacy of pre- vs. postprandial monitoring for achieving glycemic control in women with GDM.  
• 66 women with GDM who required insulin therapy at ≤30 weeks gestation were randomized to have their diabetes managed based on either preprandial or postprandial monitoring for the duration of their pregnancy; both groups also monitored their fasting blood glucose levels.  
• Compared with the preprandial group, women in the postprandial group had significantly greater A1C reductions from the time insulin therapy was initiated to delivery (−3.0 ± 2.2% vs. −0.6 ± 1.6%); mean A1C values decreased from 8.9 ± 3.2% to 6.5 ± 1.4% in the postprandial group and from 8.6 ± 2.3% to 8.1 ± 2.2% in the preprandial group.  
• Infants born to women in the postprandial group had significantly lower birth weight (3,469 ± 668 g vs. 3,848 ± 434 g), a significantly reduced risk of being large for gestational age (12% vs. 42%), a significantly lower incidence of cesarean section delivery due to cephalopelvis disproportion (12% vs. 36%), and a lower rate of neonatal hypoglycemia (3% vs. 21%) compared with infants born to those in the preprandial group. |
### Feasibility Study

**Feasibility study assessed whether BGM was effective in maintaining normal blood glucose levels during pregnancy in insulin-dependent patients with diabetes.**

- 10 women with insulin-dependent diabetes diagnosed prior to pregnancy were recruited at ≤8 weeks gestation and followed through delivery; patients were instructed to perform ≥5 BGM measurements daily, including before breakfast and dinner, and 1 hour after each meal with diet and/or insulin dose adjustments based on BG levels.

**Mean 24-hour plasma glucose levels were decreased from 169 mg/dL (9.4 mmol/L) at start to 86 mg/dL (4.8 mmol/L) within 1 week and were maintained within the normal range through delivery.**

- Mean A1C levels were reduced from 9.4 ± 1.6% at start to normal range (2.0-5.0%) 5 weeks after normoglycemia was established.

- Infants exhibited no signs of macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia, or respiratory distress.

### Abbreviations:

- A1C = glycated hemoglobin
- BG = blood glucose
- BGM = blood glucose monitoring
- CGM = continuous glucose monitoring
- GDM = gestational diabetes mellitus
- MAGE = mean amplitude of glycemic excursions
- SDBG = standard deviation of blood glucose
- MODD = mean of daily differences
- T1DM = type 1 diabetes mellitus
- T2DM = type 2 diabetes mellitus

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*Maintaining normal blood glucose levels during pregnancy in patients with diabetes is feasible and may lead to improved outcomes.*
Appendix B
Glucose Monitoring Case Studies/Patient Profiles

Case Study: Glucose Monitoring in Adult Patients With Type 1 Diabetes

Marie is a 24-year-old Caucasian woman with a 12-year history of type 1 diabetes mellitus (T1DM). She presents today to discuss how to better control her diabetes. In the past 2 years, since graduating from college and taking a demanding sales position, Marie has found it increasingly difficult to control her blood glucose levels. Marie uses neutral protamine Hagedorn (NPH) twice daily and “sliding scale” regular insulin before meals, a regimen unchanged since her diagnosis. Her previous health care professional recommended blood glucose testing before meals and at bedtime, but Marie does not adhere to this schedule. Instead, she “guesstimates” her regular insulin doses based on carbohydrate counting.

Marie was diagnosed with T1DM at age 12 after being admitted to a local hospital with symptoms of diabetic ketoacidosis. Current medications include insulin, oral contraceptives, and occasional ibuprofen for dysmenorrhea. Marie’s physical exam was normal, with the exception of bilateral background diabetic retinopathy. Laboratory tests were significant for blood glucose 276 mg/dL (15.3 mmol/L), glycated hemoglobin (A1C) 10.8%, urine albumin 42 mg/g, and creatinine 1.1 mg/dL (0.06 mmol/L). The ranges and interpretation of albumin values are shown in Table B1.

<table>
<thead>
<tr>
<th>Table B1</th>
<th>Interpretation of Albumin Values (Quest Reference Ranges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random collection (mg/g creatinine)</td>
<td>24-hour collection (mg/24 h)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td>30-300</td>
<td>30-300</td>
</tr>
<tr>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Management
Marie has poorly controlled T1DM and diabetic retinopathy. The patient was advised to undertake a continuous glucose monitoring (CGM) session. Based on data obtained (Fig. B1), Marie was advised to begin frequent blood glucose monitoring (BGM), according to the schedule summarized in Table B2.

![Fig. B1. Marie’s 24-hour continuous glucose monitoring profile prior to initiating regular blood glucose monitoring.](image-url)
**Table B2**

Recommendations for Daily Blood Glucose Monitoring in Patients With Type 1 Diabetes (31,32)

<table>
<thead>
<tr>
<th>Timing</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGM should be performed by all patients using insulin (minimum of twice daily and ideally at least before any injection of insulin)</td>
<td>FPG &lt;110 mg/dL (6.11 mmol/L)</td>
</tr>
<tr>
<td>More frequent BGM after meals or in the middle of the night may be required for insulin-taking patients with frequent hypoglycemia, patients not at A1C targets, or those with symptoms</td>
<td>2-hour PPG &lt;140 mg/dL (&lt;7.8 mmol/L)</td>
</tr>
<tr>
<td>Patients not requiring insulin therapy may benefit from BGM, especially to provide feedback about the effects of their lifestyle and pharmacologic therapy; testing frequency must be personalized</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A1C = glycated hemoglobin; BGM = blood glucose monitoring; FPG = fasting plasma glucose; PPG = postprandial glucose.

In addition to her BGM data and based on available clinical evidence, Marie was a good candidate for CGM and an insulin pump (33). The patient was prescribed an insulin pump with insulin aspart and was referred to a certified diabetes educator/pump trainer for a refresher in BGM and CGM/pump training.

Marie returned for follow-up 1 month after her initial consultation. She now routinely performs BGM 4 to 6 times per day. Figure B2 shows her daily BGM readings; a remarkable improvement in control can be observed. Marie is happy with the insulin pump and the improvements in her glucose control. Her most recent A1C was 7.6%, representing substantial progress.

![Figure B2. Marie's glycemic profile after initiating self-monitoring of blood glucose. Each line indicates a single day's glucose readings; gray ovals indicate the patient was in optimal range; black ovals indicate that the patient was out of range.](image)
Case Study: Glucose Monitoring in Pediatric Patients With Type 1 Diabetes

Leah, an 8-year old girl who participated in a randomized controlled real-time (RT) CGM study, was diagnosed at 1 year of age with T1DM. She also has celiac disease. Leah uses an insulin pump, and her A1C was 8.1% at the start of the study. This is higher than her clinic’s target of <7.5%. As illustrated by her CGM profiles below (Fig. B3), Leah also had wide glycemic fluctuations. After Leah experienced 1 episode of severe overnight hypoglycemia, her parents became more conservative in the management of her nighttime blood glucose control. Therefore, Leah’s overnight blood glucose levels were often in the 200 to 300 mg/dL (11.1-16.7 mmol/L) range.

The clinician showed Leah’s parents the high, low, and widely fluctuating glucose levels on the report (modal day report or sensor daily overlay) and explained what they meant. This created a baseline for the patient’s CGM use. At subsequent visits, the clinician worked with Leah and her parents to use the retrospective reports to adjust pump settings. These reports provided the information needed to discuss calibration technique, alarm thresholds, and treatment of low or high glucose levels. Review of the daily summary added some insight into how the family was treating low glucose in relation to the sensor reading and low trend arrows. For example, in the morning, instead of giving 4 ounces of juice, they were disconnecting Leah’s pump for 2 hours. High glucose trends followed soon after. Prompted by what was seen in the sensor daily overlay/modal day report, the clinician discussed ways to reduce the glucose variability.

Leah wore the RT-CGM for 1 year, and over that time her diabetes control improved dramatically (Fig. B4). Leah’s A1C decreased to 6.8%, there was no increase in the frequency of hypoglycemia, and her glucose variability was substantially reduced. These improvements in glycemic control were partly due to routine retrospective data review and refinement of pump settings by the clinician and her parents. In addition, by having RT sensor data, Leah was able to avoid some hypoglycemia and more promptly correct high glucose levels.
Leah had to overcome a number of practical barriers to using RT-CGM. Due to her young age and small size, her buttocks served as both her insulin pump and glucose sensor sites. Finding enough space for both of these devices is a problem for many children. Leah is a competitive swimmer, which also complicated RT-CGM use. However, RT glucose data helped Leah’s mother monitor her glucose poolside. Unfortunately, the chlorinated water often caused the sensor tape to peel off. While there were times when Leah took a break from wearing the sensors, she was very determined and would only take a few days off from sensor use. Despite these practical challenges, Leah and her family found that RT-CGM provided considerable benefit.

Case Study: Glucose Monitoring in Adult Patients With Type 2 Diabetes

Gabriela is a 68-year-old Hispanic female with a 24-year history of type 2 diabetes mellitus (T2DM). She was referred for consultation to better manage her diabetes, which was characterized by wide blood glucose fluctuations (from 60-340 mg/dL [3.3-18.9 mmol/L]) and episodes of afternoon hypoglycemia. Gabriela’s treatment regimen included glimepiride 4 mg twice a day and 40 units of insulin glargine at dinnertime.

Gabriela’s past medical history was pertinent for primary hypothyroidism, dyslipidemia, hypertension, and chronic renal failure (being treated by a nephrologist). Gabriela is a well-appearing, overweight Hispanic woman. On exam, she has background diabetic retinopathy and signs of diabetic neuropathy (10-g monofilament shows mildly diminished sensation in both feet), trace pedal edema, and 1+ pulses. Gabriela’s laboratory tests are significant for reduced hemoglobin and hematocrit (11.8/34%), elevated creatinine (1.84 mg/dL [0.1 mmol/L]; estimate glomerular filtration rate 48), blood glucose 232 mg/dL (12.9 mmol/L), A1C 10.2%, and significant proteinuria (1,654 mg/day).

At her initial visit and in anticipation of establishing a regular BGM schedule, Gabriela was advised to undergo CGM. The results from this CGM session are shown in Figure B5.

![Figure B5. Gabriela’s continuous glucose monitoring profile prior to initiating self-monitoring of blood glucose.](image)

Each line indicates a single day’s glucose readings.

At her next visit, Gabriela’s treatment was discussed. The sulfonylurea was discontinued, and she was offered several insulin treatment options, including a basal-bolus regimen or continuous subcutaneous insulin infusion (CSII) pump therapy. Gabriela chose an insulin pump with insulin lispro. She was counseled on the importance of BGM and instructed to check her blood glucose levels before meals, at bedtime, and at other times as needed. She was also referred to a certified diabetes educator to learn how to use the insulin pump.
Ten weeks after Gabriela’s initial consultation, her A1C had fallen to 8.6%. Figure B6 shows Gabriela’s 24-hour BGM profile after 10 weeks on her new regimen. Because of her chronic renal failure, pump settings were cautiously adjusted with the goal of avoiding hypoglycemic events. The patient’s overnight data were good, but from 9 AM on (after breakfast) she had high postprandial excursions on many days, a common pattern in patients with T2DM. These readings are indicative of carbohydrate ingestion not adequately addressed with medication adjustment. Gabrielle’s postdinner data also provide a good example of inadequately managed pre- and postprandial glucose and indicate that the patient needs to increase premeal insulin before dinner to address her carbohydrate intake. Typically, this adjustment is based on the following formula: 1 U insulin per × grams (e.g., 10 grams) carbohydrates.

For this patient, CSII with frequent self-monitoring of blood glucose resulted in overall improvement of glucose management and a reduction in A1C. Additional adjustments are anticipated and will be introduced over a reasonable time frame. Specifically, this study should be repeated in approximately 3 months, and it is important that the patient continue SMBG testing. Using SMBG results to drive treatment decisions is essential; treatment decisions should not be made based on CGM data points.

Case Study: Glucose Monitoring in Pregnancy Complicated by Diabetes

Pauline is 39 years old and 12 weeks pregnant. Her previous infants were large for gestational age. Her last 3 pregnancies ended with spontaneous abortion, and she has experienced a 20-pound weight gain over the last 3 years. She has a family history of T2DM, but Pauline had never been previously diagnosed with gestational diabetes mellitus (GDM) or T2DM.

Pelvic ultrasound revealed a 2-week intrauterine growth delay. Pauline was febrile, her body mass index was 34 kg/m², blood pressure 145/90 mm Hg, and her blood glucose was 348 mg/dL (19.3 mmol/L). Pauline’s urine was positive for ketones, increased protein, and numerous red and white blood cells. Pauline was diagnosed with T2DM and suspected urinary tract infection, admitted to the hospital, and started on insulin and antibiotics.
**Management**

During the hospitalization, Pauline met with a diabetes educator to begin training in BGM and insulin administration. She was instructed to check her blood glucose at least 6 times per day, as summarized in Table B3.

<table>
<thead>
<tr>
<th>Timing</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Test on waking</td>
<td>60-90 mg/dL (3.3-5.0 mmol/L)</td>
</tr>
<tr>
<td>Preprandial Test before every meal</td>
<td>60-90 mg/dL (3.3-5.0 mmol/L)</td>
</tr>
<tr>
<td>1-hour postprandial Test 1 hour after every meal</td>
<td>100-120 mg/dL (5.6-6.7 mmol/L)</td>
</tr>
</tbody>
</table>

To achieve optimal glycemic control (A1C <6.0%), Pauline was prescribed a basal/bolus insulin regimen. Pauline’s regimen included rapid-acting insulin lispro before each meal and long-acting insulin detemir. Table B4 details insulin formulations approved for use in pregnancy.

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting (aspart, lispro)</td>
<td>15 min</td>
<td>30-90 min</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Short-acting (regular human insulin)</td>
<td>30-60 min</td>
<td>2-4 h</td>
<td>5-8 h</td>
</tr>
<tr>
<td>Intermediate-acting (NPH)</td>
<td>1-3 h</td>
<td>8 h</td>
<td>12-16 h</td>
</tr>
<tr>
<td>Long-acting (detemir)</td>
<td>1 h</td>
<td>None</td>
<td>8-24 h</td>
</tr>
</tbody>
</table>

Commentary

Pauline previously delivered 2 infants with macrosomia, a clear indication of pregnancy complicated by GDM. Women who have had GDM have a 35 to 60% chance of developing T2DM in the subsequent 10 to 20 years. During this pregnancy, it is likely that Pauline had undiagnosed T2DM and uncontrolled hyperglycemia during fetal organogenesis, which places infants at high risk for congenital defects and death.

Hospitalization can ensure rapid glycemic control, but a rigorous program of BGM and insulin therapy is required to reduce the risk of complications associated with second- and third-trimester hyperglycemia. Patients should carefully record their BGM results daily to identify blood glucose patterns and adjust diet and insulin accordingly. In women with suboptimal BGM skills or experience, health care professionals should review their regimen and BGM techniques in detail.

Clinicians should encourage patient self-reliance by asking them to present, analyze, and discuss their blood glucose diaries at each visit. Frequent clinic visits can provide patients with the motivation needed to perform regular blood glucose testing. Therefore, a follow-up visit every week with a primary care physician or nurse educator can be an important component in maintaining good blood glucose control.

Steps should be taken to anticipate and prepare for disruptions in dietary routines such as dinner parties or religious fasts. Because many patients perform their most meticulous monitoring in the days leading up to their visits, clinicians should...
weigh these results in particular when making treatment decisions. Insulin dosage decisions should be based on the worst blood glucose of the day, not the best. It may also be important to address the dawn phenomenon, which is potentiated by pregnancy; patients whose fasting blood glucose is >90 mg/dL (≥5.0 mmol/L) will require an evening dose of long-acting insulin. Finally, patients like Pauline who present with probable T2DM will require postpartum re-evaluation and continued diabetes care.

Pregnant patients with diabetes of any type can use this monitoring and treatment approach to control hyperglycemia and reduce the risk of neonatal complications.

REFERENCES


