Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus: Comparative Effectiveness

Prepared for:
Agency for Healthcare Research and Quality (AHRQ)
www.ahrq.gov
Outline of Material

- Introduction to insulin delivery and glucose monitoring methods for managing diabetes
- Systematic review methods
- The clinical questions addressed by the comparative effectiveness review
- Results of studies and evidence-based conclusions about the comparative effectiveness and safety of insulin delivery and glucose monitoring methods
- Gaps in knowledge and future research needs
- What to discuss with patients and their caregivers

Diabetes mellitus is a group of metabolic diseases resulting from defects in insulin secretion from the pancreatic beta-cells, resistance to insulin action at the tissue level, or both.

The prevalence of diagnosed diabetes in the United States is currently 7.7 percent and is expected to increase to nearly 10 percent by 2050.

Type 1 diabetes accounts for 5 to 10 percent of diabetes cases in the United States; it results from the inability to produce insulin due to autoimmune destruction of pancreatic islet cells.

Type 2 diabetes accounts for 90 to 95 percent of diabetes cases; it results from a combination of insulin resistance and impaired insulin secretion by pancreatic beta-cells.

The hyperglycemia of diabetes, if untreated, can lead to long-term microvascular and macrovascular complications including:

- Retinopathy
- Nephropathy
- Neuropathy
- Coronary heart disease
- Cerebrovascular disease

In pregnant women with pre-existing diabetes, poor glycemic control is associated with poorer pregnancy outcomes including:

- Fetal anomalies
- Macrosomia
- Stillbirth
- Neonatal hypoglycemia
- Increased referral for C-section

Management of diabetes depends on the type of diabetes:

- For patients with type 1 diabetes, daily insulin therapy is vital.
- For patients with type 2 diabetes, treatment is with lifestyle modifications and/or oral medications and, if necessary, insulin.

For patients requiring insulin therapy, glycemic control with intensive insulin therapy has been shown to reduce the risk of the microvascular and macrovascular complications of diabetes.

For tight glycemic control, insulin is administered according to the basal-bolus strategy, either via multiple daily injections (MDI) or as continuous subcutaneous insulin infusion (CSII) via an insulin pump.

However, tight glycemic control can increase the risk of hypoglycemia and compromise the quality of life.

Additionally, intensive insulin therapy can lead to weight gain.

Long-term glycemic control (over 2–3 months) in individuals with type 1 or type 2 diabetes is assessed by measuring hemoglobin A$_1$c (HbA$_1$c) in the blood.

Strategies for monitoring blood glucose regularly and achieving glycemic control, particularly in patients using MDI or CSII, include:

- Self-monitoring of blood glucose (SMBG)
- Real-time continuous glucose monitoring (rt-CGM)

The most widely used SMBG technique is the fingerstick method.

rt-CGM systems provide continuous monitoring and real-time feedback to patients on their blood glucose levels.

Sensor-augmented pumps that combine rt-CGM systems with CSII are also available.

SMBG allows timely feedback on hyperglycemia and has been shown to be a component of successful diabetes management.

- The American Diabetes Association (ADA) recommends that SMBG should be carried out three or more times a day in patients using MDI or CSII.
- Pain associated with the SMBG approach affects adherence to this technique.

rt-CGM can be useful in detecting fluctuating blood glucose levels in some patient populations.

- According to the ADA, rt-CGM may be a supplemental tool to SMBG in patients with hypoglycemia awareness or frequent hypoglycemic episodes.
- Similarly, the success of rt-CGM depends on adherence to the continuous use of this device.
The benefits and harms of insulin delivery with CSII versus MDI in patients with type 1 or type 2 diabetes and in pregnant women with pre-existing diabetes are not completely known.

Additionally, the relative benefits of glucose monitoring with SMBG versus rt-CGM in these populations have not been thoroughly evaluated.

Given the new technologies in insulin delivery and glucose monitoring, clinicians are faced with challenges in determining which modalities are most beneficial to their patients.

Therefore, the comparative effectiveness and/or adverse effects of the modes of insulin delivery (CSII vs. MDI) and glucose monitoring (rt-CGM vs. SMBG) requires systematic review.

Topics are nominated through a public process, which includes submissions from health care professionals, professional organizations, the private sector, policymakers, lay persons, and others.

A systematic review of all relevant clinical studies is conducted by independent researchers, funded by AHRQ, to synthesize the evidence in a report summarizing what is known and not known about the select clinical issue. The research questions and the results of the report are subject to expert input, peer review, and public comment.

The results of these reviews are summarized into Clinician Research Summaries and Consumer Research Summaries for use in decisionmaking and in discussions with patients. The Research Summaries and the full report, with references for included and excluded studies, are available at www.effectivehealthcare.ahrq.gov/glucose.cfm.
Key Question 1: In patients receiving intensive insulin therapy, does mode of delivery (CSII vs. MDI) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

Clinical Questions Addressed by the Comparative Effectiveness Review (2 of 2)

Key Question 2: In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)?

Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?
d. Intensive insulin delivery: MDI or CSII?

The strength of evidence was classified into four broad categories:

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit estimation of an effect.</td>
</tr>
</tbody>
</table>

HbA\textsubscript{1c} lowering did not differ significantly between CSII and MDI (mean difference from baseline, -0.14%; 95% confidence interval [CI], -0.48 to 0.20; \( p = 0.41 \)).

Strength of Evidence: Moderate

Frequency of daytime hypoglycemia, frequency of nocturnal hypoglycemia, rate of severe hypoglycemia, weight gain, and quality of life did not differ significantly between CSII and MDI.

Strength of Evidence: Low

CSII was associated with a significant improvement in diabetes treatment satisfaction versus MDI (mean difference, 5.7; 95% CI, 5.0 to 6.4; \( p < 0.001 \)).

Strength of Evidence: Low

CSII resulted in a significant HbA$_{1c}$-lowering effect when compared with MDI (mean difference from baseline, -0.30%; 95% CI, -0.58 to -0.02), although results were heavily influenced by one study.

Strength of Evidence: Low

Frequency of nocturnal hypoglycemia, severe hypoglycemia, other nonsevere hypoglycemia, hyperglycemia, and weight gain did not differ significantly between CSII and MDI.

Strength of Evidence: Low

CSII resulted in a small decrease in postprandial glucose and an increase in symptomatic hypoglycemia when compared with MDI.

Strength of Evidence: Low

CSII was associated with a significant improvement in diabetes-specific quality of life when compared with MDI (mean difference, 2.99; 95% CI, 0.006 to 5.97; $p = 0.05$).

Strength of Evidence: Low

HbA$_{1c}$ lowering did not differ significantly between MDI and CSII (mean difference from baseline, -0.16%; 95% CI, -0.42 to 0.09; $p = 0.21$).

Strength of Evidence: Moderate

The risk of mild hypoglycemia was lower with CSII versus MDI; however, there was no significant difference between the two groups (combined relative risk, 0.90; 95% CI, 0.78 to 1.03).

Strength of Evidence: Moderate

No significant between-group differences in frequency of severe hypoglycemia or in weight gain were observed in this population.

Strength of Evidence: Low

Insulin Delivery With MDI Versus CSII in Pregnant Women With Pre-existing Diabetes

- \( \text{HbA}_1c \) improved in both the CSII and MDI arms in all three trimesters, with no significant differences between the two arms.
  Strength of Evidence: Low

- The strength of evidence for all other findings related to pregnant women with pre-existing diabetes (including maternal hypoglycemia, maternal weight gain, rate of cesarean sections, and neonatal outcomes) were rated as insufficient.

rt-CGM was associated with a significant HbA$_1$c-lowering effect when compared with SMBG (mean difference from baseline, -0.30%; 95% CI, -0.37 to -0.22%; $p < 0.001$).

Strength of Evidence: High

Time spent in the hypoglycemic range was similar in the rt-CGM and SMBG groups (mean difference, 2.11 minutes/day; 95% CI, -5.66 to 1.44 minutes/day).

Strength of Evidence: Moderate

A significant reduction in the time spent in the hyperglycemic range occurred with rt-CGM when compared with SMBG (-68.56 minutes/day; 95% CI, -101.17 to -35.96).

Strength of Evidence: Moderate

The evidence was inconsistent for the effect of rt-CGM versus SMBG on the ratio of basal to bolus insulin in a daily insulin dose.

Strength of Evidence: Low

The rt-CGM and SMBG groups exhibited similar rates of severe hypoglycemia, general quality of life and diabetes-specific quality of life.

Strength of Evidence: Low

Using a sensor-augmented pump is associated with a significant HbA$_{1c}$-lowering effect when compared with SMBG in children and adults with type 1 diabetes (mean difference from baseline, -0.68%; 95% CI, -0.81 to -0.54%; $p < 0.001$).

Strength of Evidence: Moderate

Time spent with nonsevere hypoglycemia and incidence of severe hypoglycemia were similar between the sensor-augmented pump and the MDI/SMBG groups.

Strength of Evidence: Moderate

Overall diabetes treatment satisfaction was greater among participants in the sensor-augmented pump arm when compared with the MDI/SMBG arm; there is no significant difference in weight gain between the two arms.

Strength of Evidence: Low

Evidence from two randomized controlled trials suggests that time spent with hyperglycemia is significantly lower in the sensor-augmented pump group versus the MDI/SMBG group ($p < 0.001$).

Strength of Evidence: Moderate
Both CSII and MDI had similar effects on glycemic control and rates of severe hypoglycemia in children and adolescents with type 1 diabetes and adults with type 2 diabetes.

- In contrast, some studies suggested that CSII was superior to MDI for glycemic control in adults with type 1 diabetes with no difference in hypoglycemia and weight gain.

Limited evidence suggested that measures of quality of life or treatment satisfaction improved in patients with type 1 diabetes.

- The approach to intensive insulin therapy can, therefore, be individualized to patient preference to maximize quality of life.

rt-CGM was superior to SMBG in lowering HbA$_{1c}$, without affecting the risk of severe hypoglycemia, in nonpregnant individuals with type 1 diabetes.

- This effect was greater when compliance with rt-CGM was high.

Sensor-augmented pumps were superior to MDI/SMBG in lowering HbA$_{1c}$ in the research studies analyzed in this review.

- However, other combinations of these insulin delivery and glucose monitoring modalities were not evaluated.

Knowledge Gaps and Future Research Needs (1 of 3)

- Most randomized controlled trials identified in the literature for inclusion in this review were small.
- Most studies were fair to poor in quality and did not report most outcomes of interest.
- Most studies did not report the racial and ethnic composition of the study populations; for those that did, most participants were white.
- Few studies focused on, or included, children 12 years of age or younger or adults 65 years of age or older.
- The studies included in this review varied widely in their definitions of nonsevere hypoglycemia, hyperglycemia, and weight gain, thus preventing definitive conclusions about the effects of insulin delivery and glucose monitoring strategies on these outcomes.

- None of the studies included data on the long-term microvascular and macrovascular complications of diabetes.

- The studies in pregnant women with pre-existing type 1 diabetes did not examine the effect of rt-CGM on maternal and fetal outcomes.

- Most of the included studies, particularly those comparing MDI with CSII, did not report on the extent of treatment adherence, which may have biased the results.

- The studies were not uniform in assessing and reporting quality-of-life outcomes, thus precluding quantification of the effects of insulin delivery and glucose monitoring devices on quality of life.
Several studies excluded individuals with comorbidities, thereby limiting the applicability of the results to the entire population.

The identified gaps in this review highlight the need for future well-designed studies with:

- Large study populations including all age-groups and diverse ethnicities
- Long followup periods
- Standard outcome measures, including measures of vascular complications and quality of life
- Studies of pregnant women with pre-existing type 1 and type 2 diabetes

What To Discuss With Your Patients and Their Caregivers (1 of 2)

- The type of his/her diabetes and the potential role of insulin therapy in its treatment
- The role of other lifestyle changes in managing the patient’s diabetes
- The importance of glycemic control in managing the patient’s diabetes
- The role of routine blood glucose monitoring in maintaining appropriate glycemic control and in managing the patient’s diabetes
- The importance of having a sick-day regimen in order to avoid extreme hypoglycemic or hyperglycemic episodes in times of illness or inability to eat
- The available strategies for insulin delivery and blood glucose monitoring

What To Discuss With Your Patients and Their Caregivers (2 of 2)

- The available evidence for the effectiveness of MDI versus CSII for insulin delivery
- The available evidence for the effectiveness of SMBG versus rt-CGM for glucose monitoring
- The patient’s preferences with regard to the mode of insulin delivery and glucose monitoring
- The available evidence for the effectiveness of rt-CGM plus CSII (sensor-augmented pump) versus MDI/SMBG
- The potential risks associated with intensive insulin therapy such as hypoglycemic events and weight gain, their impact on quality of life, and strategies for their management
- The potential out-of-pocket costs that the patient might incur based on his/her insurance coverage with each option.