New Technologies for Insulin Administration and Glucose Monitoring

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Keypoints

- Continuous subcutaneous insulin infusion pumps and continuous glucose monitors can be effective tools for improving metabolic control in patients with type 1 diabetes.
- Pump therapy provides increased lifestyle flexibility, and can reduce the risk for hypoglycemia.
- Real-time continuous glucose monitoring devices provide detailed information on glucose patterns and trends, and alarms that are triggered by both hyperglycemia and hypoglycemia.
- Randomized trials indicate that this technology can lead to a reduction in HbA1c without an associated increase in hypoglycemia.

Introduction

The development of capillary blood glucose monitors set the stage for the era of intensive insulin therapy, and technologic advances continue to be an important driver for improvements in diabetes care. In this chapter we highlight the developments of the past decade focusing on those technologies that show the most promise in improving the lives of people with diabetes, in particular, insulin pump therapy and real-time continuous glucose monitoring. In recent years, inhaled insulin has been an area of intense investigation; however, interest in this mode of insulin delivery has been diminished by concerns about potential pulmonary toxicity.

Continuous subcutaneous insulin infusion pumps

Continuous subcutaneous insulin infusion (CSII) pumps were first introduced over 30 years ago [1,2]. They consist of an insulin reservoir and a delivery catheter that continuously infuses insulin into the subcutaneous tissue. In recent years, there has been growing adoption of this technology in diabetes care. Several factors have contributed to this increased use, including the focus on intensive therapy triggered by the Diabetes Control and Complications Trial (DCCT); improvements in the reliability and usability of pumps; patient preferences; and also the growing recognition by clinicians that CSII delivery is associated with reduced risk for hypoglycemia. Because a comprehensive review of insulin pump therapy is beyond the scope of this chapter, we focus on issues that have received most attention in the recent literature, including the potential advantages of pumps as a tool for insulin administration and newer developments in pump technology such as bolus calculator software. In addition, we provide some practical pointers about pump therapy for the clinician.

Glycemic control with insulin pumps compared with multiple daily insulin injections

Several published meta-analyses have examined the role of CSII pumps as a tool for intensifying glycemic control [3–5]. These meta-analyses of the randomized controlled trials in the published literature indicate that CSII use in patients with type 1 diabetes mellitus (T1DM) is associated with 0.4–0.5% (5–6 mmol/mol) lower HbA1c than multiple daily injection (MDI) therapy. The improvements in HbA1c with the change to pump therapy appear to be greater in individuals who have poorer glycemic control [6,7]. Most of the studies examined in these meta-analyses involved MDI regimens using NPH or ultralente insulins; however, more recent randomized controlled trials suggest that CSII is also superior to MDI regimens using the newer long-acting insulin analogs [8,9]. Data about potential complications of pump therapy (such as ketoacidosis, pump malfunction and insulin site problems) is not reported in many of the published randomized trials, and most evidence suggesting that CSII is associated with an increased risk for ketoacidosis date from the 1980s [10–12]; however, device malfunction and infusion site problems
do still occur with modern pump technology, which points to the importance of giving education on proper catheter site care and ketoacidosis prevention to all patients using pumps.

Because of the more controlled delivery of insulin, CSII can be an effective tool for reducing glycemic variability, and this can be of benefit for reducing the risk for hypoglycemia brought about by insulin replacement therapy [13]. Clinical guidelines from several national and international organizations recommend consideration of pump therapy for individuals with T1DM with suboptimal glycemic control and problematic hypoglycemia (Box 28.1) [14–16]. However, conclusions from the meta-analyses about whether the mode of insulin delivery has an impact on hypoglycemia have yielded conflicting results [5,17,18], in large part because of methodologic issues and differences in trial selection [19,20]. The meta-analysis of randomized controlled trials by Pickup & Sutton [17], which was restricted to studies published since 1995 (i.e. since the introduction of more reliable pump technology) with a baseline (pre-trial) rate of severe hypoglycemia of ≥10 episodes/100 patient years and ≥6 months of CSII use, showed that there was a 2.9-fold (95% confidence interval [CI] 1.45–5.76) reduction in severe hypoglycemia during CSII compared to MDI. The analysis also indicated that the benefit from pump therapy was greater in individuals with higher rates of severe hypoglycemia (P < 0.001) and those with longer duration of diabetes (P = 0.025) [17]. A meta-analysis commissioned by the Endocrine Society reached different findings, and concluded that in comparison with MDI, CSII was not associated with a significant reduction in severe or nocturnal hypoglycemia [18]. The validity of these conclusions is limited by the inclusion of studies of relatively short duration with low incidence rates of severe hypoglycemia that would bias against the detection of any potential benefit from pump therapy. In addition, the rates of minor and nocturnal hypoglycemia were determined using intermittent fingerstick glucose monitoring, which can be unreliable in detecting nocturnal hypoglycemic events [21] and would therefore be relatively insensitive to detecting treatment-related differences. Furthermore, it should also be noted that the studies examined in this analysis were almost entirely performed using older pump types that did not incorporate the bolus calculator software now available in updated pumps which can help to limit hypoglycemia related to doses stacking up from repeated boluses. These factors limit the generalizability of the conclusions from this analysis to clinical practice, and the weight of evidence from studies reported in the literature suggest that clinicians caring for motivated patients with T1DM who have recurrent hypoglycemia and especially a history of severe hypoglycemic reactions should recommend a trial of insulin pump therapy.

Evidence in insulin-requiring type 2 diabetes mellitus (T2DM) regarding the potential benefits of pump therapy in comparison with MDI is limited. The studies of Raskin et al. [22] and Herman et al. [23] showed similar HbA1c changes with both modes of insulin delivery. A small-scale cross-over study in obese subjects with T2DM with insulin resistance has demonstrated a significant reduction in HbA1c and postmeal glucose excursion with use of pump therapy [24]. Where patients are unable to achieve adequate glycemic control, several practical issues should be considered (Box 28.2).

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**Box 28.1 Pump therapy: indications and considerations**

- **Severe hypoglycemia and hypoglycemia unawareness**
- **HbA1c above goal**
  - **Caution:** Intentional insulin omission (to facilitate weight loss) is a not uncommon cause for poorly controlled diabetes, especially in young women [32]. Before initiating pump therapy, it is important to rule out this problem. Because these patients habitually underdose insulin and are frequently hyperglycemic, they do not routinely troubleshoot for insulin non-delivery by the pump and can therefore be at increased risk for developing ketoacidosis.
- **Diurnal variations in basal insulin requirements caused by the dawn phenomenon [33,34] and steroid therapy can be more readily managed using the multiple basal rates provided by the pump than by long-acting injected insulins [35].** Continuous subcutaneous insulin infusion can be of special benefit for the post-renal transplant diabetes patient on steroid therapy who is striving for intensive glycemic control.
- **Preconception and pregnancy**
- **Practical advantages of pumps for bolus insulin delivery** include:
  - **Dosing precision:** The extra precision of insulin dosing with pumps can be an important advantage for young children (especially infants and neonates) [36] and adults who are on very low insulin doses. In addition, accurate dosing of insulin boluses in fractions of a unit allows the patient to correct hypoglycemia more precisely without overshooting and causing hypoglycemia. For those patients in whom fear of hypoglycemia is an impediment to tight glycemic control, this added assurance can be critical in overcoming reluctance to intensification. In practice, it can be helpful to reduce missed food boluses, facilitate interprandial “correction” bolusing, and help simplify eating at restaurants and social occasions (with the use of extended/square wave boluses and multiple bolusing).
  - **Optimizing post-prandial insulin coverage:** Facilities dosing for higher fat, complex carbohydrate and/or larger meals. Dietary fat delays gastric emptying [37] and induces post-prandial insulin resistance [38], so high-fat meals cannot usually be adequately covered using a single injection of rapid-acting insulin [39]. Use of the extended/dual bolus and increased temporary basal can help optimize post-prandial glycemic control following these meals [40–42]. (For practical strategies see Wolpert [43].)
  - **Gastroparesis:** Use of the extended/dual wave bolus can allow for better matching of carbohydrate absorption and insulin action.
Many patients describe improvements in quality of life when they change to pump therapy; however, there have been few carefully designed studies that have examined patient perspectives of pump therapy, and differences in psychosocial functioning with CSII compared to MDI [4,25]. The published literature suggests that use of pumps is associated with improved quality of life compared to MDI [26–28]; however, this has not been confirmed in all studies [29]. Patients will vary in their perceptions about the potential quality of life benefits (including increased lifestyle flexibility, dietary freedom, reduced fear for hypoglycemia) relative to some of the potential drawbacks of CSII (including body image concerns and the need for frequent blood glucose monitoring) [30]. Wolpert and colleagues conducted a focus group investigation of 30 patients followed at the Joslin Diabetes Center to examine how psychosocial factors impacted the use of the pump [31]. Patients with better glycemic control viewed the pump as a tool for diabetes self-management rather than as a panacea. In contrast, the pump patients with poorer HbA1c had more unrealistic expectations including the perception that use of technology was a substitute for attentiveness to self-care and that pump therapy allowed them to do whatever they wanted, particularly with regard to eating. Before initiating pump therapy, health care professionals need to assess patients’ expectations of the pump, dispel unrealistic notions (often promoted by marketing materials) and ensure that patients recognize that while the pump allows life with diabetes to be more flexible and convenient, it is not a vehicle for total freedom from diabetes.

Box 28.2 Practical issues to consider in the pump patient with erratic glucose control

- Infusion site issues including scarring, lipohypertrophy and lipoatrophy: Infusion sites should be routinely examined in pump users with unexplained glucose fluctuations
- Infusion catheter kinking or dislodgement: Plastic catheters that are perpendicular to the skin surface and have a small base for attachment (e.g. Medtronic MiniMed Sofset™, Disetronic Ultraflex™) are more prone to kink or become dislodged especially with activity or perspiration. Solutions include changing to metal needle infusion sets, plastic sets with a shorter cannula, or other types of plastic infusion sets that are less prone to kinking. These include the Medtronic MiniMed Quickset™ (which has a broad base of attachment to the skin), and sets that insert obliquely such as the Medtronic MiniMed Silhouette™, Roche Disetronic Tender™ and Animas Comfort™
- Failure to change the pump reservoir and infusion system on a regular basis: This may manifest in a tendency for elevated and erratic glucose in the period preceding infusion set changes
- Review of pump downloads can be helpful:
  - Check priming history to assess how frequently the infusion system is being changed
  - Check bolus history to detect possible missed meal boluses
  - Check percentage of basal to bolus insulin. A high percentage of basal insulin in the patient with frequent hyperglycemia may indicate that bolus doses are frequently being missed. A high percentage of basal insulin in the patient with frequent hypoglycemia may indicate that high basal rates are contributing to hypoglycemia, and would point to a need to re-evaluate basal rate settings
  - Check for a history of pump suspension or basal rate reduction. Even temporary removal of the pump to bathe can lead to elevations in the glucose levels; patients need to be reminded to bolus to replace the missed basal when reconnecting the pump. Some patients using the pump will get in the practice of reducing the basal rate or suspending the pump when they are hypoglycemic; the end result will often be exaggerated rebound hypoglycemia
- Insulin instability in the pump infusion system: This can manifest as increases in the glucose levels in the period preceding infusion set changes or even precipitation in the infusion system [46]
- Pump malfunction
- Air bubbles in infusion system resulting from poor filling technique

Quality of life benefits and patient expectations

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consideration in setting the insulin duration of action in the bolus calculator software is usually a best guess based on a clinical assessment of the hypoglycemia risk of the patient and the imperative for achieving tight glycemic control (in particular, preconception and pregnancy) [45]. For individuals with frequent hypoglycemia, hypoglycemia unawareness or a history of severe hypoglycemic reactions, the duration of action should be set 5 hours or even longer, whereas for the woman who is pregnant or trying to conceive, the duration of action is often set at 2–3 hours. The glucose records of the patient can be assessed to determine if the duration of action settings are appropriate. If the duration of action time programmed into the software is less than the true duration of action, the pump will indicate that there is less IOB than is actually the case, and the patient will mistakenly take more insulin than required; the glucose records will show evidence of hypoglycemia from “stacking” of doses. Conversely, if the setting programmed into the pump is longer than the true duration of insulin action, this can lead to underdosing of insulin and hinder attempts to optimize glycemic control.

Real-time continuous glucose monitoring

In the last several years, several real-time continuous glucose monitoring (RT-CGM) devices (Abbott Freestyle Navigator®, DexCom Seven®, Medtronic Guardian®/Paradigm® system) have received the CE mark and approval from the US Food and Drug Administration (FDA) for long-term use in ambulatory patients with diabetes (Figure 28.1). These devices have transcutaneous glucose oxidase-based electrochemical sensors that measure the glucose concentration in the interstitial fluid every 1–5 minutes (Figure 28.2). Because of accuracy limitations [47,48], the current

Figure 28.1 Three components of continuous glucose monitoring (CGM) device: sensor, transmitter and receiver unit.

Figure 28.2 Modal day report from patient who eats breakfast at 9:00 am and supper at 10:00 pm daily. Indicates rapid spike in glucose levels post-meal that had not been detected with intermittent fingerstick blood glucose monitoring. Treatment recommendations focused on changing to more slowly absorbed lower glycemic index carbohydrates (e.g. oatmeal) and/or injection of bolus insulin earlier before the meal.
generation of CGM devices do not have regulatory approval for use as stand-alone devices, and patients are required to perform adjunctive capillary blood glucose measurements; however, this limitation is compensated by the additional detailed information provided by the CGM about glucose patterns, the rate and direction of change in the glucose level and adjustable alarms that are triggered by both hyperglycemia and hypoglycemia (Figure 28.3) [49].

Clinical efficacy of RT-CGM

Because RT-CGM is a relatively new technology, to date only a few randomized controlled trials have been performed. The initial reported studies, which were only several days in duration, showed that use of RT-CGM leads to a reduction of both hyperglycemic and hypoglycemic excursions with more time in the target glucose range [50,51]. The GuardControl trial using the Medtronic Guardian was the first longer duration study of RT-CGM. This study enrolled 156 adults and children with T1DM using both pumps and MDI therapy [52]. At 3-month follow-up, the group randomized to RT-CGM use had 1.0 ± 1.1% (11 ± 12 mmol/mol) reduction in HbA1c, (down from 9.5 ± 1.1% [80 ± 12 mmol/mol] at baseline) compared to 0.4 ± 1.0% (5 ± 11 mmol/mol) reduction in the control group (P = 0.003). In addition, at 3 months, 50% of subjects in the CGM group had HbA1c reductions of ≥1% compared to 15% of subjects in the control group, and 26% in the CGM group had HbA1c reductions of ≥2% compared to 4% in the control arm. Reported results from this industry-supported study have not included any specific information on the treatment protocols used in the trial or data about the effect of CGM on hypoglycemia.

To date, the results of two large-scale multicenter randomized controlled trials of 6 months’ duration have been published in the literature: the industry-supported Star 1 trial and the Juvenile Diabetes Research Foundation (JDRF) sponsored CGM trial. The Star 1 trial enrolled 146 subjects aged 12–72 years with T1DM treated with CSII pumps [53] who were randomized to pump therapy with RT-CGM using the Medtronic 722 pump system or pump therapy with fingerstick self-monitoring of blood glucose. The primary endpoint was not achieved; there was a similar reduction in HbA1c (0.71 ± 0.71% in the sensor group vs 0.56 ± 0.072% in the control group; P = non-significant) over the 6-month trial. Importantly, in the subjects using RT-CGM, the improvement in glycemic control was accomplished without any
change in biochemical hypoglycemia \( (P < 0.0002) \), whereas in the control subjects using fingerstick glucose monitoring there was an increase in biochemical hypoglycemia (documented with blinded CGM devices). More severe hypoglycemic events occurred in the group using RT-CGM than in the control group (11 vs 4; \( P = 0.04 \)). During six of the 11 severe events in the RT-CGM group, subjects were not using a sensor. The Data Safety Monitoring Board determined that in the remaining five severe hypoglycemic events there was evidence of the following: 1 Failure of subjects to respond to alarm warnings of hypoglycemia; 2 Multiple insulin boluses without use of the pump bolus calculator, resulting in dose stacking; or 3 “Blind boluses” (i.e. treatment decision based on sensor readings showing hyperglycemia without confirmatory fingerstick capillary blood glucose measurements). This clinical experience from the Star 1 trial was incorporated into the treatment protocols and patient education materials used in the JDRF CGM trial.

The JDRF CGM trial enrolled 451 patients with T1DM aged 8–74 years and HbA1c <10\% (86 mmol/mol) to a RT-CGM group or control group that continued with capillary blood glucose monitoring \([54,55]\). This study involved patients using both insulin pumps and injection therapy and used three different CGM devices (Abbott Navigator®, Dexcom Seven® and Medtronic Guardian/722® system), with assignment based on patient preference with investigator guidance. By design, the cohorts with HbA1c at randomization of ≤7.0\% (<53 mmol/mol; \( n = 129 \)) and 7–10\% (53–80 mmol/mol; \( n = 322 \)) were analyzed separately.

For individuals with T1DM who have already managed to achieve HbA1c levels in the optimal target range with intermittent capillary blood glucose monitoring, the main therapeutic challenge is minimizing the risk for hypoglycemia that accompanies intensive glucose control. Accordingly, for the cohort enrolled in this trial with baseline HbA1c <7.0\% (<53 mmol/mol), the pre-specified primary endpoints were focused on changes in hypoglycemia rather than HbA1c per se. At 26 weeks, biochemical hypoglycemia ≤3.9 mmol/L (70 mg/dL) was less frequent in the CGM group than the control group using intermittent fingerstick monitoring (median 54 vs 91 minutes/day), but this was not statistically significant. Median time spent with glucose level ≤3.3 mmol/L (60 mg/dL) was 18 vs 15 minutes/day, respectively \( (P = 0.05) \). There were similar numbers of severe hypoglycemic events in the two groups; however, the trial was not adequately powered to detect a treatment group difference. More subjects in the CGM group than the control group had a decrease in HbA1c of ≥20\% without having a severe hypoglycemic event (28\% vs 5\%; \( P < 0.01 \) \([56]\).

For the cohort with baseline HbA1c 7–10\% (53–86 mmol/mol), the pre-specified primary endpoint was HbA1c reduction. A significant between-group difference in change in HbA1c from baseline to 26 weeks was seen in patients ≥25 years old, favoring the continuous monitoring group (mean difference in change −0.53\%; \( P < 0.001 \)), but not in the younger subjects. Biochemical hypoglycemia evaluated by CGM was similar in the two treatment groups. Similarly, there were no significant differences in the incidence of severe hypoglycemic events between the study groups. In the adult cohort, the frequency of the combined outcome of 26-week HbA1c <7.0\% (<53 mmol/mol) and no severe hypoglycemic events was 30\% in the CGM group and 7\% in the control group \( (P = 0.0006) \)[55]. This finding, that RT-CGM leads to an improvement in glycemic control without an associated worsening in hypoglycemic events, is in direct contrast to other intervention studies such as the DCCT in which intermittent capillary glucose monitoring had been used to guide intensification of metabolic control, and points to the promise this new technology offers for people with T1DM.

### Practical issues with use of RT-CGM

The randomized controlled trials that have demonstrated the benefits of RT-CGM have involved patients with a high level of engagement in their diabetes self-care (mean number of daily capillary blood glucose measurements performed by subjects enrolling in the JDRF trial was six). Furthermore, to use this technology successfully, patients need to have advanced diabetes self-management skills (Box 28.3). In the next sections we discuss several key issues that need to be addressed in the training of patients starting on CGM.

### Physiologic lag between blood and interstitial glucose

The lag in the equilibration of glucose levels between the capillary blood (measured using home blood glucose monitoring device) and the interstitial fluid in the subcutaneous tissue (measured by the CGM device) \([57,58]\) has important practical implications. In general, increases or decreases in the glucose concentration will first be apparent in the blood followed by the interstitial fluid. Currently available CGM devices are calibrated using fingerstick capillary blood glucose measurements, and to optimize sensor accuracy it is important that the device only be calibrated when the glucose level is relatively stable, and there is steady-state equilibration between glucose concentrations in the blood and interstitial fluid. In practice, calibrations should be performed

### Box 28.3 Patient teaching points: Adjusting bolus doses based on rate of change of glucose \([63]\)

- If glucose ↑ by 0.056–0.11 mmol/L/minute (1–2 mg/dL/minute): +10\% to calculated food/correction bolus
- If glucose ↑ by >0.11 mmol/L/minute (>2 mg/dL/minute): +20\% to calculated food/correction bolus
- If glucose ↓ by 0.056–0.11 mmol/L/minute (1–2 mg/dL/minute): −10\% from calculated food/correction bolus
- If glucose ↓ by >0.11 mmol/L/minute (>2 mg/dL/minute): −20\% from calculated food/correction bolus

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preprandially or at least 3 hours after a bolus (Box 28.4). The first generation CGM devices need to be calibrated at least 4 times per day for optimal accuracy [59].

The physiologic lag has implications with regard to detection and treatment of hypoglycemia. Because of the lag of interstitial glucose behind blood glucose, when the glucose level is declining the interstitial (sensor) glucose can be in the normal range even though the actual blood glucose is low [60]. Patients should be instructed to perform a fingerstick blood glucose measurement before driving if the sensor reading is normal and the trend graph or rate-of-change arrows on the sensor display indicate that the glucose level is declining (Box 28.5). As shown in the study by Wilson et al. [61], when the glucose is falling rapidly, the physiologic lag can also lead to underestimation by the rate-of-change indicator of the CGM device. The practical implication is that if the patient feels hypoglycemic or has reason to suspect that the glucose is declining, but this is not corroborated by the sensor, they should disregard the sensor data and carry out a fingerstick glucose measurement.

This lag phenomena also has practical implications for the treatment of hypoglycemia. During the recovery from hypoglycemia, the increase in the interstitial glucose will often lag behind the blood glucose [62], and at a time when blood glucose has already normalized the sensor/interstitial glucose may still be in the low range. Patients should be instructed of the need to perform fingerstick glucose measurements to assess the response to treatment of hypoglycemia accurately. Patients who rely on the RT-CGM to judge whether the glucose level is improving following ingestion of carbohydrates will mistakenly assume that they need to consume more.

Setting glucose alarms

The alarms for hypoglycemia and hyperglycemia are an important feature of RT-CGM devices. There are trade-offs in the adjustment of alarm thresholds, and settings need to be individualized based on specific clinical considerations [64]. If the alarm thresholds are set at target or ideal glucose levels (e.g. low = 5 mmol/L [90 mg/dL]; high = 10 mmol/L [180 mg/dL]), there will be increased sensitivity for detection of high and low glucoses; however, the frequent false alarms can be a source of irritation and disrupt sleep leading to “alarm fatigue” in some patients with a related tendency to ignore the alarms (Figure 28.4).

The adjustment of alarm thresholds is a stepwise process:

1. Deciding on initial thresholds when initiating use of the sensor; and
2. Optimizing alarm thresholds over time based on retrospective review of continuous glucose tracings.

For patients with hypoglycemia, unawareness or a history of severe hypoglycemic reactions, where the overriding imperative is on reducing hypoglycemia, the low glucose alarm threshold should be set at 4.5 mmol/L (80 mg/dL) or higher. Because of physiologic lag between blood and interstitial glucose, when the sensor alarm is triggered, the blood glucose level will often be lower than the sensor measurement.

For individuals without a history of problematic hypoglycemia, it is a common practice to set the initial glucose thresholds at 3–3.5 mmol/L (55–60 mg/dL) and ≥14 mmol/L (250 mg/dL). This ensures that during the initial period after starting use of CGM, while the patient is mastering use of the technology, there will be fewer intrusive and irritating alarms, and less risk for alarm burnout. Over time, as the patient uses the information from the sensor to reduce glucose excursions, the alarm settings can be brought closer to target glucose levels, and this can assist with further tightening of glycemic control.

During follow-up visits, the clinician should enquire whether the sensor alarm alerted the patient to low or markedly elevated glucose levels, and whether the patient was troubled by frequent false alarms. If there are frequent high glucoses (especially during the overnight period) and the patient is not being appropriately alerted by the sensor to take corrective action, the high alarm threshold should be reduced. Conversely, if the patient has experienced hypoglycemic reactions without being alerted by the

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**Box 28.4 Patient teaching points: Calibration do’s and don’ts**

- Before calibrating the sensor, the patient should check to be sure that there are no arrows on the sensor display indicating that the glucose is changing rapidly
- Calibration should not be performed:
  - Within 3–4 hours of a meal or an insulin bolus
  - During exercise
  - After recovering from hypoglycemia

**Box 28.5 Patient teaching points: Circumstances where fingerstick capillary glucose must be checked**

- If the sensor indicates that the glucose is elevated, the reading must first be confirmed with a fingerstick capillary blood glucose measurement before the patient takes a corrective bolus
- Whenever subjective symptoms are not in keeping with the sensor reading, a fingerstick reading should be taken to confirm the glucose level
- Before or during driving, if the sensor reading is normal and the continuous glucose monitoring rate of change indicator or tracing indicates that the glucose level is falling, the patient must measure fingerstick blood glucose
- Following treatment of a low glucose, if the sensor still shows a low reading, the patient should check fingerstick blood glucose and use this measurement to decide whether to take in more carbohydrate. Reliance on the sensor reading to assess response can lead to overtreatment

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do with the information. Clearly, there is inherent human error in this system and overdosing or underdosing of insulin based on a small miscalculation could result in subsequent hypoglycemic or hyperglycemic episodes, respectively. In a “closed-loop system” which integrates a continuous glucose monitor and insulin pump, together with an automated algorithm to control insulin delivery, the patient would be removed from the decision loop, and the system would essentially function as an artificial pancreas.

At present, one of the major challenges for the fully automated closed-loop system may be in the development of a fail-safe algorithm that is capable of “interpreting” a person’s metabolic state based on data obtained from the continuous glucose monitor and then relaying this information to the pump for automatic insulin delivery of the appropriate dose of insulin. Several algorithms including model predictive control and proportional integral derivative control are already being evaluated in both in vivo and in silico settings [66]. There are also several technical obstacles to developing a closed-loop system including having glucose sensors that are both accurate and reliable (e.g. minimal calibration drift, limited potential mechanisms for sensor failure), and also physiologic lag which can be particularly problematic during times of rapid rates of change in blood glucose levels (e.g. during meals or exercise) [67]. Thus, development of a sensor with a short lag time would also be important. The first prototype closed-loop systems that can deliver glucagon to prevent hypoglycemia are currently being evaluated [68].

Development of the first generations of an artificial pancreas is underway and several studies have already demonstrated that glycemic control can be achieved with an automated closed loop system in investigational and controlled hospital settings [69–72]. Medtronic MiniMed has developed an external physiologic

Risk for hypoglycemia from excessive post-prandial bolusing

While the glucose alarms and trend indicators on CGM devices can be helpful in minimizing hypoglycemia, some patients will overreact to the post-prandial glucose spikes revealed by the continuous sensor by taking excessive doses of insulin [65], leading to an increased risk for hypoglycemia. Minimizing this tendency for post-prandial overbolusing should be a major focus in the training of the patient using RT-CGM. Patients need to factor in the amount of residual IOB from the previous bolus before taking additional insulin to treat post-prandial hyperglycemia. The newer pumps with bolus calculator software can guide patients in making appropriate dose adjustments.

The glycemic index of the carbohydrates in the meal is another factor to consider in the decision about whether additional boluses may be required to treat post-prandial hyperglycemia. High glycemic index carbohydrates will often lead to an early spike in the glucose levels (because of the mismatch between the absorption of the carbohydrate and action of the insulin bolus), and correction boluses taken within 2–3 hours after the meal can result in hypoglycemia.

Closed-loop/Artificial pancreas

Insulin pump therapy as it is currently used is considered to be an “open-loop system,” in which the patient must make executive decisions about when to check the glucose level and what to do with the information. Clearly, there is inherent human error in this system and overdosing or underdosing of insulin based on a small miscalculation could result in subsequent hypoglycemic or hyperglycemic episodes, respectively. In a “closed-loop system” which integrates a continuous glucose monitor and insulin pump, together with an automated algorithm to control insulin delivery, the patient would be removed from the decision loop, and the system would essentially function as an artificial pancreas. At present, one of the major challenges for the fully automated closed-loop system may be in the development of a fail-safe algorithm that is capable of “interpreting” a person’s metabolic state based on data obtained from the continuous glucose monitor and then relaying this information to the pump for automatic insulin delivery of the appropriate dose of insulin. Several algorithms including model predictive control and proportional integral derivative control are already being evaluated in both in vivo and in silico settings [66]. There are also several technical obstacles to developing a closed-loop system including having glucose sensors that are both accurate and reliable (e.g. minimal calibration drift, limited potential mechanisms for sensor failure), and also physiologic lag which can be particularly problematic during times of rapid rates of change in blood glucose levels (e.g. during meals or exercise) [67]. Thus, development of a sensor with a short lag time would also be important. The first prototype closed-loop systems that can deliver glucagon to prevent hypoglycemia are currently being evaluated [68].

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insulin delivery system that combines an external insulin pump and continuous glucose sensor with a variable insulin infusion rate algorithm designed to emulate the physiologic characteristics of the β-cell. Similar devices by other companies, including Abbott Laboratories, are also being developed and tested.

**Inhaled insulin**

Survey studies have indicated that fear of needles and discomfort and inconvenience from injecting insulin are barriers to the use of insulin by many patients with T2DM [73,74]. An effective alternative mode for insulin administration would therefore be of potential benefit. As insulin is a peptide hormone, it cannot be taken orally, as it would be quickly degraded by the digestive enzymes of the stomach. Alternative routes of administration that have been investigated include transdermal, transbuccal and transpulmonary (inhaled) delivery of insulin.

The lung is an attractive mode for administration of a systemic drug because of its large available area for drug absorption and accessibility. In January 2006, the FDA approved the use of Exubera® (Pfizer), the first inhalable insulin.

Clinical studies have shown that pre-meal inhaled insulin achieves comparable glycemic control to subcutaneous regular insulin administration [75–77]; however, smoking can significantly alter the pharmacokinetics of inhaled insulin [78,79], and even passive smoke exposure in non-smokers can affect bioavailability [80]. Follow-up of the patients who had used Exubera in clinical trials has raised concerns about the potential long-term toxicity of insulin delivered by the pulmonary route. As of April 2008, six of the 4740 patients who used Exubera in clinical trials had developed lung cancer, compared with only one of the 4292 patients in the placebo group. All six patients with lung cancer had a prior history of cigarette smoking (Exubera label, FDA approval September 29, 2008), and this association was not statistically significant because of the small numbers. However, because of these safety concerns, as well as failure of Exubera to gain acceptance by patients and physicians, Pfizer withdrew Exubera from the market, and Eli Lilly and Novo Nordisk also gave up their efforts to develop their own insulin inhalation systems.

At present, one company, MannKind Corporation, has continued to develop an inhalable insulin, Technosphere® insulin [81]. In March 2009, a new drug application to market this insulin was filed with the FDA. Technosphere insulin contains insulin particles that are optimized for inhalation (2.5 μm in diameter) and dissolve rapidly after inhalation (pH sensitive carrier particles). Pharmacokinetic studies have demonstrated that this formulation has very rapid systemic insulin uptake (insulin T_max approximately 12–14 minutes), a fast onset of action (maximum activity approximately 20–30 minutes) and a short duration of action (approximately 2–3 hours) [82] which could potentially provide better post-prandial control than subcutaneously injected insulin.

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