

# Pitfalls in Outpatient Diabetes Management

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**Editor's note:** This article is the 10th in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the Clinical Diabetes website (<http://clinical.diabetesjournals.org>).

The challenges of treating patients with diabetes are many. Patients usually require oral medications and/or insulin to control glucose levels. Such medications require careful titration as well as monitoring for side effects or adverse reactions. Additionally, patients must be educated and motivated by their caregivers to monitor glucose levels, control carbohydrate consumption, and aggressively participate in self-care to control their disease. Such treatment allows patients to minimize the likelihood that they will develop chronic complications of diabetes such as microvascular or macrovascular disease.

In addition to the usual challenges regarding diabetes control, diabetes can also be exacerbated by factors such as medication changes, surgery, and illnesses. Such conditions can lead to acute decompensation of glucose control even in the setting of previously well-controlled disease. Acute complications of diabetes such as diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) may develop, which can be

life-threatening and must be treated aggressively.<sup>1</sup>

Although it is important for physicians to understand the treatment of acute complications of diabetes, it is perhaps even more important to be versed in techniques of averting acute hyperglycemia. Three common causes of diabetes exacerbation include intercurrent illness, surgery or trauma, and use of corticosteroids.

## Intercurrent Illness

Intercurrent illnesses can be challenging to any patient with a chronic disease, but they are especially problematic in patients with diabetes. Such conditions exacerbate hyperglycemia, and even patients with well-controlled diabetes may develop considerable hyperglycemia.

Infections have long been recognized as a major cause of acute hyperglycemia, DKA, and HHS.<sup>1,2</sup> Hyperglycemia in response to infection likely takes place as a result of several pathogenic mechanisms. Gram-negative lipopolysaccharide has been shown to increase insulin resistance significantly, possibly mediated through increase in stress hormones such as cortisol and growth hormone.<sup>3</sup> Because patients with diabetes are unable to increase insulin production and release to compensate for increased insulin resistance, hyperglycemia worsens during such infections. Early recog-

nition and treatment is essential to avoiding DKA or HHS.

Patients with diabetes should be taught sick-day procedures when they are initially diagnosed with diabetes to prepare them for such illnesses. Hyperglycemia frequently develops before infectious symptoms and should serve as a warning that infection could be developing. Those using insulin note a progressive increase in insulin requirements over hours or days as infection develops. To control glucose levels, patients using rapid- or short-acting insulin must rely on correction insulin doses to a greater extent than usual. If hyperglycemia is progressive or severe, often they must use rapid- or short-acting insulin every 4 hours to avoid severe hyperglycemia. This may include setting alarms to wake them overnight to check glucose and administer additional insulin. If hyperglycemia remains despite these measures, the magnitude of the correction dose algorithm must be increased to compensate for increased insulin resistance.

Patients with type 2 diabetes using oral medications who experience infection also experience hyperglycemia, although the degree of hyperglycemia may be less severe depending on their insulin secretory reserve. Patients early in the course of type 2 diabetes may have sufficient  $\beta$ -cell mass to increase insulin production and therefore may experience only slight hyperglycemia during infection. Others with longstand-

ing type 2 diabetes and presumably a greater degree of  $\beta$ -cell depletion may have little capacity to produce additional insulin to compensate for increased insulin resistance and therefore experience profound hyperglycemia during infection.

Such patients therefore need additional treatment during infection, typically in the form of insulin because oral agents require weeks or longer to reach full effect. In addition to preventing DKA and HHS, insulin therapy will help prevent dehydration, which can occur quickly when glucose levels exceed renal threshold ( $\sim 180$  mg/dl) and therefore induce diuresis. Patients should be advised to maintain adequate hydration during hyperglycemia.

Patients developing illness must also be cautious about metformin. Metformin is associated with a low but significant risk of lactic acidosis in the setting of acute illness including urosepsis, renal insufficiency, and hypovolemia.<sup>4</sup> Patients who use metformin should be instructed to discontinue it in the event of illness that could lead to hypovolemia or dehydration. Discontinuing metformin during a time of increased insulin resistance can lead to further hyperglycemia; therefore, patients may require initiation of insulin therapy during such episodes.

Correction insulin usually is given in the form of rapid- or short-acting insulin at meals. A typical algorithm for type 1 diabetes might be to add 1 extra unit of insulin to the usual mealtime dose per 50 mg/dl that blood glucose rises above the target range; for type 2 diabetes, the algorithm might be to add 1 unit per 30 mg/dl above target range, although some patients will require higher doses. Basal insulin would require several days to achieve steady-state pharmacokinetics and therefore is not as effective in the

acute setting. If illness is anticipated to be prolonged, however, starting basal/bolus therapy with both rapid- and long-acting insulin may be warranted. It is important to note, however, that hospitalized patients with type 2 diabetes using correction doses alone experience more hyperglycemia than patients using basal/bolus insulin.<sup>5</sup>

Patients beginning insulin should be instructed about the signs, symptoms, risks, and treatment of hypoglycemia and reminded of the importance of neither driving nor operating machinery while hypoglycemic. Additionally, patients with type 1 diabetes and established insulin requirements should not be placed on sliding scale only.<sup>6</sup>

#### **Outpatient Surgical Glucose Control**

Surgery, like illness, can increase glucose levels probably through stress hormone release as well as mediators of inflammation. Furthermore, surgical patients who experience significant hyperglycemia ( $> 220$  mg/dl) on the first postoperative day are at a significantly higher risk to develop postoperative infection.<sup>6,7</sup> Hospitalized patients who experience new hyperglycemia and patients with known diabetes have higher in-hospital mortality rates.<sup>6,8</sup>

Patients therefore need proper adjustment of their diabetes regimen before surgery. Such adjustment is complicated by the fact that many diabetes medications cannot be adequately used or adjusted in the perioperative state. As previously noted, metformin may not be used in periods of acute illness, hypoperfusion, or hypoventilation. Patients undergoing surgery are at risk for such illness and therefore must stop taking metformin when undergoing surgical procedures.<sup>4</sup> Metformin may be restarted when patients are eating and drinking normally after

surgery and have adequate renal, hepatic, and cardiac function.

Insulin secretagogues such as sulfonylureas and meglitinides (glyburide, glipizide, glimipiride, nateglinide, and repaglinide) stimulate insulin release from  $\beta$ -cells and can produce hypoglycemia in the fasting state or when carbohydrate consumption is decreased. They are difficult to titrate acutely and may also have delayed onset of action as well as prolonged effects. Therefore, they usually are not used in the perioperative setting.

Thiazolidinedione medications have a very delayed effect of 2–3 months or longer and therefore cannot be titrated acutely. They also exhibit the potential side effects of liver dysfunction and exacerbation of heart failure. Glucagon-like peptide 1 agonists and dipeptidyl peptidase-4 inhibitors also stimulate insulin release from  $\beta$ -cells and help suppress hepatic gluconeogenesis but have significant gastrointestinal side effects and a very limited inpatient record. Because of these limitations, insulin is the drug of choice to manage glucose in the perioperative period.<sup>6</sup>

If it is clear that a patient will need insulin when stopping oral agents (such as in patients on multiple oral agents), it is sometimes advisable to transition to insulin therapy before hospitalization. Basal/bolus insulin, consisting of long-acting insulin to control fasting glucose levels and rapid-acting insulin at mealtimes (with a correction factor), has been proven effective in hospitalized patients.<sup>5,6</sup> Such regimens allow patients to adjust insulin based on their degree of hyperglycemia and amount of carbohydrate intake and may also pose a lower risk of hypoglycemia because mealtime doses can be held for lack of appetite.

One of the most challenging aspects of controlling glucose levels after surgery, whether in inpatient

or outpatient settings, is matching rapid- or short-acting insulin administration to carbohydrate consumption. Patients frequently have lessened carbohydrate intake after surgery and hospitalization compared to before, and rapid- or short-acting insulin doses must reflect such dietary changes.

For patients already managing glucose levels before surgery, emphasis should be placed on counting grams of carbohydrate and using an insulin-to-carbohydrate ratio to determine mealtime doses. If patients are beginning insulin in the perioperative period, a brief review of carbohydrate counting techniques may be helpful. Patients who are unable or unwilling to count carbohydrate grams may be amenable to adjusting their mealtime insulin dose based on the size of their meal, although such an approach may be somewhat prone to glucose level fluctuation. Patients should also be advised to hold their mealtime insulin if they are not eating and may administer their mealtime insulin after a meal if their appetite or ability to eat is in question. Although they may seem challenging, covering tube feedings with insulin may be relatively straightforward because grams of total carbohydrate are usually printed on cans of enteral feeding formula.

Another advantage of basal/bolus insulin therapy is the ability to titrate patients' correction insulin and mealtime doses relatively quickly. As discussed previously, insulin sensitivity decreases significantly during acute illness such as surgery but gradually returns to baseline. Insulin doses may be increased after surgery to accommodate a patient's needs and then gradually titrated back to baseline as

tolerated. Oral agents may be gradually resumed as tolerated.

Patients with an established insulin requirement should not rely solely on a correction dose algorithm as their only insulin treatment because such treatment may exacerbate glucose fluctuations. A full discussion of inpatient diabetes and insulin management is beyond the scope of this article but will be addressed in the next installment of this series.

Because surgery and a limited ability to eat frequently increases glucose fluctuations, patients should be reminded of the signs, symptoms, risks, and treatment of hypoglycemia. They should have available a source of easily absorbable simple carbohydrates such as juice or glucose tablets to use in the event of hypoglycemia. Patients who have impaired ability to eat or swallow (such as patients with gastric bypass or enteral feedings) should have glucagon on hand for administration in the event of hypoglycemia. Because insulin sensitivity sometime increases rapidly when a patient is recovering from surgery, patients should be especially aware of the possibility of hypoglycemia during recovery and as their activity level increases.

### **Glucocorticoids**

Glucocorticoid therapy is very common and efficacious for innumerable medical conditions. Glucocorticoids, however, can cause significant side effects such as hyperglycemia and overt diabetes. One study suggests that as many as 2% of the incident cases of type 2 diabetes are related to use of oral glucocorticoids. The same study suggests that other forms of glucocorticoid therapy such as ocular formulations, inhalers, and topical preparations are not associated with incidence of diabetes on a population level.<sup>9</sup>

Glucocorticoids induce hyperglycemia via several mechanisms. They

increase glucose production from the liver, interfere with  $\beta$ -cell function, and inhibit glucose uptake by cells. The degree of resulting hyperglycemia can vary from patient to patient, with some patients developing mild hyperglycemia and others developing dangerously high glucose levels, DKA, or HHS. Although there is no absolute predictor to determine which patients develop hyperglycemia from glucocorticoids, the best predictors include family history of diabetes, increased age, and dosage of the glucocorticoid administered.<sup>10</sup>

Patients who develop hyperglycemia from glucocorticoids often experience disproportionate postprandial hyperglycemia. Thiazolidinediones have been shown to help control hyperglycemia from glucocorticoids, but their side effect profile and slow rate of effectiveness in such patients limit their usefulness. Insulin is used most often for glucocorticoid-induced hyperglycemia.

Because the predominant problem often is postprandial hyperglycemia, prandial insulin may yield the best glucose control.<sup>10</sup> If the duration of treatment with glucocorticoids is brief, patients may respond well to a mealtime dose of rapid- or short-acting insulin with a correction dose addition if glucose is elevated. If more prolonged therapy with glucocorticoids is anticipated, teaching an insulin-to-carbohydrate ratio may be advisable to reduce the risk of insulin-to-carbohydrate mismatch and resultant glucose fluctuations.

As in recovery from surgery, care must be taken to decrease insulin administration as glucocorticoids are tapered. If glucocorticoid doses are large or prolonged (more than 2 weeks), physicians should also be cognizant of the possibility of adrenal insufficiency, which can dramatically decrease insulin requirements and is associated with dangerous hypoglycemia.

Other signs of adrenal insufficiency include increased fatigue, weight loss, nausea, and diarrhea. Presence of repeated hypoglycemia despite reduction in therapy should prompt physicians to consider ordering an adrenal stimulation test to evaluate for adrenal suppression from exogenous glucocorticoids.

Diabetes, like other diseases, can fluctuate in severity. One of the most difficult aspects of diabetes care is controlling such fluctuations in glucose control. Doing so requires a great deal of diligence and anticipation on the part of both physicians and patients. Common causes of exacerbations in glucose control include infections, surgical procedures, and the use of glucocorticoid-containing medications. Such situations may lead to worsening of glucose control, and it is important to be aware of what measures should be undertaken to regain glucose control when glucose rises acutely. Such precautions can help prevent more serious events such as severe hyper-

glycemia, hypoglycemia, DKA, and HHS.

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**Note of disclosure:** *Dr. Fowler has served as a speaker for and received grant support from Novo Nordisk, which manufactures insulin products for the treatment of diabetes.*