Pitfalls in Outpatient Diabetes Management and Inpatient Glycemic Control

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Editor's note: *This article is the sixth in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in* Clinical Diabetes *between 2006 and 2009. The previous series, and earlier installments of this one, can be found online at the journal Web site (http://clinical.diabetesjournals.org).*

The challenges of treating patients with diabetes are many. Patients usually require oral medications, insulin, or both to control glucose levels. Such medications require careful titration and monitoring for side effects and adverse reactions. Additionally, care providers must educate and motivate patients to monitor their glucose levels, control their carbohydrate consumption, and aggressively participate in self-care to control their disease. These treatments allow patients to minimize the likelihood of developing chronic complications of diabetes such as micro- or macrovascular disease.

In addition to the usual challenges, diabetes can also be exacerbated by less common factors such as medication changes, surgery, and illness. Such conditions can lead to acute decompensation of glucose control even in the setting of previously well-controlled disease. Acute complications such as diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) may develop. These conditions can be life-threatening and must be treated aggressively.[1]

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 the use of corticosteroids.

Furthermore, inpatient diabetes and hyperglycemia management can be complicated and present unique challenges to care providers. Approximately 12–25% of hospitalized patients have diabetes, and the diagnosis of diabetes at hospital admission has increased 2.3-fold to 5.1 million from 1980 to 2003. Numerous studies have associated hyperglycemia with adverse outcomes during hospitalization; however, interventional studies that have attempted to decrease such complications by aggressively treating hyperglycemia have had mixed outcomes.[2,3]

This installment of our series on the fundamentals of diabetes care will review management recommendations in special outpatient situations and inpatient diabetes care.

Intercurrent Illness

Intercurrent illnesses can be challenging to any patient with a chronic disease, but they are especially problematic for patients with diabetes. Such conditions exacerbate hyperglycemia; 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.[1,4] Hyperglycemia in response to infection likely is the 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.[5] Because patients with diabetes are unable to increase insulin production and release to compensate for increased insulin resistance, hyperglycemia worsens during such infections. Early recognition and treatment of this problem 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 a period of hours or days as infection develops.

To control their glucose levels, patients using short- or rapid-acting insulin must rely on their adjustment insulin ("correction dose algorithm") to a greater extent than usual. If hyperglycemia is progres-

sive or severe, they may need to use short- or rapid-acting insulin every 4 hours. This may involve setting alarms to wake them overnight to check glucose and administer additional insulin. If hyperglycemia persists despite these measures, the magnitude of the correction dose algorithm must be increased to compensate for increased insulin resistance.

Patients with type 2 diabetes who use oral medications and experience infections 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 β-cell mass to increase insulin production and therefore may experience only slight hyperglycemia during infection. Others with longstanding type 2 diabetes and presumably greater degrees of β-cell depletion may have little capacity to produce additional insulin to compensate for increased insulin resistance and therefore may experience profound hyperglycemia during infection. Such patients 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 the renal threshold (~ 180 mg/dl) and induce diuresis. Patients should be advised to maintain adequate hydration during hyperglycemia.

Patients developing illness must also be cautious regarding 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.[6] Patients should be instructed to discontinue metformin 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, in such cases, patients may require initiation of insulin therapy.

Supplemental insulin usually is given in the form of short- or rapid-acting insulin at meals with correction dose algorithm. Basal insulin would require several days to achieve steady-state pharmacokinetics and therefore not as effective in the acute setting. If illness is anticipated to be prolonged, however, starting basal/bolus therapy with both short- and long-acting insulin may be warranted.

It is important to note, however, that hospitalized patients with type 2 diabetes using adjustment insulin alone (only "correction dose algorithm") experience more hypoglycemia than patients using basal/bolus insulin.[7] Patients beginning insulin should be instructed about the signs, symptoms, risks, and treatment of hypoglycemia and reminded of the importance of not driving or operating machinery while hypoglycemic. Additionally, patients with type 1 diabetes and established insulin requirements should not be placed on correction-dose algorithm only.[8–10]

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.[8,11] Hospitalized patients who experience new hyperglycemia and patients with known diabetes experience higher in-hospital mortality rates.[8,12]

Patients therefore need proper preparation of their diabetes regimen before surgery. However, such preparation is complicated by the fact that many diabetes medications can not be adequately used or adjusted in the perioperative state.

As previously noted, metformin may not be used during periods of acute illness, hypoperfusion, or hypoventilation. Because patients undergoing surgery are at risk for such illness, metformin must be stopped at the time of surgical procedures.[6] It may be restarted when patients are eating and drinking normally after surgery and have aqequate renal, hepatic, and cardiac function.

Insulin secretagogues such as sulfonylureas and meglitinides (glyburide, glipizide, glimipiride, nateglinide, and repaglinide) stimulate insulin release from β-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 and prolonged effects. Therefore, they usually are not used in the perioperative setting.

Thiazolidinediones have a very delayed effect of 2–3 months or longer and therefore cannot be titrated acutely. They are also associated with the potential side effects of liver dysfunction and exacerbation of heart failure.

Glucagon-like peptide 1 agonists and dipeptidyl peptide IV inhibitors also stimulate insulin release from β-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.[8] For patients who clearly will need insulin when stopping oral agents (such as those using multiple

oral agents), it is sometimes advisable to transition to insulin therapy before hospitalization.

Basal/bolus insulin, consisting of slow-acting insulin to control fasting glucose levels and fast-acting insulin at mealtime with a correction factor ("correction-dose algorithm") has been proven effective in hospitalized patients.[7,8] Such regimens allow patients to adjust insulin based on their degree of hyperglycemia and carbohydrate intake. They may also lower the risk of hypoglycemia because mealtime insulin doses can be withheld for lack of appetite.

One of the most challenging aspects of controlling glucose levels following surgery, whether in inpatient or outpatient settings, is matching short- or rapid-acting insulin administration to carbohydrate consumption. Patients frequently have lower carbohydrate intake after surgery and hospitalization compared to before, and short- or rapid-acting insulin 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 rather than estimating doses of insulin. If patients are beginning insulin in the perioperative period, brief review of carbohydrate counting techniques may be helpful. If they are unable or unwilling to count carbohydrate grams, patients may be amenable to adjusting their mealtime insulin doses according to the size of their meals, although such an approach may lead to a greater degree of glucose fluctuation. Patients should also be advised to hold their mealtime insulin if they are not eating or to take their mealtime insulin after meals if their appetite or ability to eat is in question. Although it may seem challenging, covering tube feedings with insulin is often relatively straightforward in that the 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 use only a correction factor (algorithm) as their only insulin treatment because such an approach may exacerbate glucose fluctuations.

Because surgery and irregular eating frequently lead to increased glucose fluctuations, these patients should be also be reminded of the signs, symptoms, risks, and treatment of hypoglycemia. They should have easily absorbable sources of simple carbohydrate available (e.g., juice or glucose tablets) to use in the event of hypoglycemia. If patients have impaired ability to eat or swallow (e.g., patients with gastric bypass or enteral feedings), they should have glucagon on hand because they may be more limited in their ability to quickly consume carbohydrates to treat hypoglycemia. Because insulin sensitivity sometimes increases rapidly when patients are recovering from surgery, they should be especially aware of the possibility of hypoglycemia during recovery and as their activity level increases.

Glucocorticoids

Glucocorticoid therapy is 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 incident cases of type 2 diabetes are related to the use of oral glucocorticoids. The same study suggests that other forms of glucocorticoid therapy (e.g., ocular formulations, inhalers, and topical preparations) are not associated with incident diabetes on a population level.[13]

Glucocorticoids induce hyperglycemia via several mechanisms. They increase glucose production from the liver, interfere with β-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 of which patients will develop hyperglycemia from glucocorticoids, the best predictors include a family history of diabetes, increasing age, and dosage of glucocorticoid.[14]

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

Because the predominant problem is often postprandial hyperglycemia, prandial insulin may yield the best glucose control.[14] If the duration of treatment with glucocorticoids is brief, patients may respond well to mealtime doses of short- or rapid-acting insulin with correction doses if their 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 (> 2 weeks), providers should 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. The presence of repeated hypoglycemia despite reduction in therapy should prompt providers to consider ordering an adrenal stimulation test to evaluate for adrenal suppression from exogenous glucocorticoids.

Inpatient Diabetes Management

Observational studies

It has long been observed that patients with diabetes or who develop hyperglycemia in response to stress of illness may have poor hospital outcomes and higher rates of complications when hospitalized. This trend has shown itself in patients with mild degrees of illness and small surgical procedures as well as in critically ill patients and those undergoing major surgery. Recently, several studies have attempted to quantify the increased risk in patients with diabetes in the hospital setting and to measure whether aggressive intervention improves such risks.

One of the first studies that attempted to quantify the extent of increased risk to non-critically ill patients was conducted by Umpierrez et al.[12] They analyzed the hospital records of > 2,000 patients who were admitted in general hospital wards in a community hospital. The study included both medical and surgical patients. Of the patients studied, 26% had known diabetes, whereas 12% were newly diagnosed as hyperglycemic based on a fasting glucose level ≥ 126 mg/dl or random glucose measurements ≥ 200 mg/dl on two occasions. Impressively, 38% of all patients admitted into general hospital wards had diabetes or hyperglycemia, illustrating the importance of inpatient glucose management.

In this study, patients with a preexisting diagnosis of diabetes experienced a 2.7-fold increase in risk of in-hospital mortality compared to patients with normoglycemia. Perhaps even more strikingly, patients with newly diagnosed hyperglycemia had an 18-fold increase in the risk of mortality. Patients with newly diagnosed hyperglycemia were also found to have longer lengths of hospital stay, a higher risk of admission into the intensive care unit (ICU) and were less likely to be discharged to home, often requiring nursing or rehabilitation facility placement.[3,12]

The relationship between high glucose levels and poor outcomes is also true for patients with more severe illnesses such as ischemic injuries. Patients experiencing myocardial infarction (MI) with hyperglycemia have a higher risk of death than patients without hyperglycemia. Furthermore, such patients with hyperglycemia also experience a higher likelihood of congestive heart failure or cardiogenic shock compared to patients who are normoglycemic.[15] Stroke patients who are hyperglycemic also experience a higher risk of death or poor functional recovery compared to patients who do not experience hyperglycemia. One possible explanation is that hyperglycemia may increase the oxygen demands of ischemic tissue in both circumstances, thus exacerbating injury.[15,16] This information is especially salient because patients with diabetes have higher rates of stroke and MI.

In patients with diabetes who are hospitalized, there appears to be increased risk associated with higher glucose levels. Patients undergoing surgery who experience hyperglycemia with glucose > 220 mg/dl exhibit an infection rate 2.7 times higher than patients with diabetes who do not experience glucose > 220 mg/dl. Furthermore, when minor urinary tract infections are excluded, the relative risk of infection is increased to 5.7 if glucose exceeds 220 mg/dl on the first postoperative day.[11]

Trauma patients experience similar risks associated with stress hyperglycemia after hospitalization. A recent study identified a higher risk of infection and mortality rates in trauma patients who experience glucose levels > 200 mg/dl in the first 2 days after hospitalization. This association remained significant independent of injury characteristics but not for lesser degrees of hyperglycemia.[17]

Surgical patients with high glucose levels, therefore, are at elevated risk for adverse outcomes even if their glucose level is elevated in the absence of a known history of diabetes. This information helps to identify patients who are at elevated risk to develop complications while hospitalized, but perhaps a more important question may be whether normalizing glucose levels reduces such risk.

Interventional studies

Several studies have attempted to reduce morbidity and mortality of hyperglycemia through improved glucose control. The Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction study investigated whether patients with acute MI and high glucose levels would benefit from insulin and dextrose infusion

acutely, followed by intensive subcutaneous insulin therapy for 3 months after infarction. Mean blood glucose in the "conventional" group was 210.6 mg/dl, whereas in the treatment arm, the mean was 172.8 mg/dl. The study showed that with an average of 3.5 years follow-up, there was an absolute reduction in mortality of 11%, likely representing one life saved per nine patients treated.[18]

Not all studies have come to the same conclusion, however. A similar study, the Hyperglycemia: Intensive Insulin Infusion in Infarction Study, demonstrated lower incidence of cardiac failure and reinfarction within 3 months with tight glycemic control, but no overall change in mortality was noted.[2,19] Additionally, patients undergoing cardiac surgery who attain good glucose control may have reduced mortality and a lower risk of deep sternal wound infections.[2] These studies suggest that improved glucose control improves the risk of morbidity, but mortality benefit may be arguable.

In a famous study, Van den Berghe et al.[20] randomized patients with hyperglycemia (with or without a previous diagnosis of diabetes) to receive either intensive insulin therapy intravenously with a target glucose of 80–110 mg/dl or conventional therapy with a target glucose of 180–200 mg/dl. Intensive insulin therapy was associated with a significant reduction in mortality, especially in patients with multiple organ failure with a septic focus. There was a 34% reduction in overall in-hospital mortality, with a lower incidence of bloodstream infection and acute renal failure requiring dialysis and a lower number of red blood cell transfusions. However, a similar study in the medical intensive care setting[21] did not show difference in mortality but did significantly decrease morbidity by decreasing the risk of newly acquired kidney injury, accelerating weaning from mechanical ventilators, and leading to faster ICU and hospital discharge.

It should be noted that other studies have also failed to show survival benefit and have shown higher risk of severe hypoglycemia with intensive insulin therapy. The largest trial to date, the NICE-SUGAR trial, did not show benefit in intensive glucose control of critically ill surgical and nonsurgical patients and in fact may have demonstrated a higher mortality in such patients.[9,21] Furthermore, a recent meta-analysis concluded there was not a benefit in mortality from intensive glucose control.[2,9,22]

Controlling Hyperglycemia

There are many treatment options to control glucose levels in the outpatient setting. Unfortunately, few of these medications translate well into inpatient or acute-illness therapy. Some agents are ineffective in acute illness, require long periods of time to be practical in the hospital environment, or may even be detrimental when patients are seriously ill. As described previously, oral agents do not lend themselves to acute titration and are frequently contraindicated during critical illness, leaving insulin as the drug of choice for glucose control during hospitalization.

Ideally, subcutaneous insulin should be administered in scheduled doses in conjunction with a correction algorithm that allows for and helps to quantify increases in patients' insulin requirements. Patients should receive scheduled insulin of both long-acting insulin to cover basal needs and short- or rapid-acting insulin doses to cover carbohydrate consumption and other sources of carbohydrate such as intravenous dextrose, dextrose derived from dialysate, and tube enteral feedings. This may be accomplished through the use of various insulin preparations. It is important to note, however, that several intermediate-acting insulin preparations such as NPH or premixed insulin containing NPH may exceed basal insulin requirements for several hours and could cause hypoglycemia in patients who are not eating.

A correction insulin algorithm should not be used alone to control glucose levels. Use of correction insulin alone in essence waits for patients to become hyperglycemic before they are treated and may also predispose them to hypoglycemia.[2,14,23]

In acute illnesses, including DKA and HHS, intravenous regular insulin is frequently used to control hyperglycemia. It offers the advantage of a very rapid effect and a rapid dissipation of effect if stopped. Many hospital settings now have algorithms to allow their nursing staff to adjust insulin infusion rates, although no particular infusion protocol has been proven to be superior to others. Intravenous insulin may also be used as a way to qualitify insulin requirements in patients with either type 1 or type 2 diabetes.[2]

As in the treatment of DKA, patients receiving intravenous insulin infusion should resume rapid-acting insulin at meals and intermediate- or long-acting insulin when they are recovering and are able to eat a substantial amount of carbohydrate. It is important to continue intravenous insulin for several hours after resumption of subcutaneous insulin to avoid recurrent hyperglycemia and possible ketoacidosis, especially in patients with type 1 diabetes.

Controlling Hypoglycemia

Physicians should also be cautious regarding patients developing hypoglycemia in the inpatient setting. As described previously, hypoglycemia is the limiting factor in controlling

hyperglycemia. Hypoglycemia may occur with virtually any form of diabetes pharmacotherapy, so clinicians should be aware of its potential occurrence and how to treat it appropriately in both outpatient and inpatient settings.

Patients who develop renal, adrenal, hepatic, or cardiac dysfunction and those with limited nutritional intake, sepsis, or malignancy are at particularly increased risk for hypoglycemia. These patients sometimes exhibit considerable insulin sensitivity and therefore require smaller insulin doses than they were using in their outpatient regimen or than other patients with diabetes. Additionally, they may also have declining insulin requirements and therefore need frequent insulin adjustments to avoid hypoglycemia.

Patients' orders should include a treatment plan for hypoglycemia.[2] Treatment may take the form of oral carbohydrate, intravenously administered 50% glucose solution (D50), or glucagon.

General Recommendations

Based on the above and other studies and on clinical experience, the American Diabetes Association offers several guidelines regarding the management of diabetes and hyperglycemia during patients' hospitalization.[2,9]

Patients admitted into the hospital with diabetes should have diabetes clearly labeled in their medical record. Glucose monitoring should be ordered for all patients with diabetes, typically before meals and at bedtime for patients who are eating and every 4–6 hours for patients who are not eating. All patients receiving therapy for diabetes should have a plan for hypoglycemia treatment. Patients with diabetes who are critically ill should have their glucose level kept as close to a range of 140–180 mg/dl as possible, and intravenous insulin by established safe protocol is generally the best method for achieving this goal. Non–critically ill patients should receive treatment, usually in the form of subcutaneous insulin, to keep fasting glucose < 140 mg/dl and random blood glucose < 180 mg/dl.[2,9]

Because of the risk of hypoglycemia, there may be situations in which insulin treatment should be less aggressive, especially during initial treatment. Scheduled prandial doses of insulin should be administered at the appropriate times in relationship to meals to avoid glucose fluctuations. Patients should also receive correction doses of insulin when needed but should not be placed on a correction insulin algorithm alone. Hospitalized patients with hyperglycemia who do not have a previous diagnosis of diabetes should have follow-up testing after discharge.[2,9]

Diabetes, like other diseases, can fluctuate in severity. One of the most difficult aspects of diabetes care is controlling 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 fluctuations include infections, surgical procedures, and the use of glucocorticoid-containing medications. Such situations may lead to worsening of glucose control. Therefore, it is important to be aware of what measures should be undertaken to regain control when glucose rises acutely. Such precautions can help prevent more serious events such as severe hyperglycemia, hypoglycemia, DKA, and HHS before they occur in both the outpatient and inpatient settings.

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