Glycemic Control in the Hospitalized Patient with Diabetes Mellitus
Case Study and Commentary, David R. Handin, MD

Abstract
Diabetes mellitus, particularly type 2 diabetes, is an increasingly prevalent disease. Patients with diabetes are admitted to the hospital more frequently and have longer stays than nondiabetic patients. In addition, up to 15% of patients admitted to general medical services for diagnoses not directly related to diabetes have diabetes as a comorbid condition. This article reviews the approach to providing optimal care for hospitalized patients with diabetes. The use of sliding-scale insulin regimens alone poses risks to patients and is not supported by the limited literature. Moreover, there is an increasing literature demonstrating the benefits of tightening glycemic control in the acute setting for a subset of clinical scenarios.

CASE 1
Initial Presentation
A 65-year-old woman with type 2 diabetes is admitted for evaluation of chest pain that has occurred 3 times in the past 24 hours, most recently when walking across her bedroom just prior to presentation.

History and Physical Examination
The patient has a history of previous poor glycemic control, but over the past 6 months she has been treated with a multidrug regimen and now has an HbA1c of 7.6% and a fasting glucose level of 105 mg/dL. She has early retinopathy, mild peripheral neuropathy, and microalbuminuria. Her serum creatinine level is normal. She has a low-density lipoprotein (LDL) level of 140 mg/dL. Her medications at home include insulin glargine (Lantus) 12 U every night, metformin, glipizide, enalapril, pravastatin, and extended-release diltiazem. Her heart rate is 80 bpm, her blood pressure is 130/75 mm Hg, and her electrocardiogram shows normal sinus rhythm with nonspecific ST-T wave changes. Her cardiac troponin I is mildly elevated with normal creatine kinase levels.

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Treatment Plan
Her clinical history is consistent with unstable angina. She is given aspirin, heparin, and made NPO for cardiac catheterization in the morning.

- What changes need to be made to the patient’s medication regimen in light of her NPO status and upcoming procedure?

In approaching her inpatient care, 2 issues regarding her outpatient medications must be addressed. The first involves adjusting or holding her glucose-lowering therapy during the NPO period. The second involves determining which other medications need to be adjusted or monitored in relation to the invasive procedure and illness.

Goals of Glycemic Management
Hypoglycemia can have serious neurological consequences. Typical early symptoms include hunger, sweating, and light-headedness. Later signs include confusion and depressed level of consciousness, which if unrecognized or untreated can progress to stupor, coma, and death. Prolonged untreated hypoglycemia can lead to irreversible neurologic damage. Many of the early signs are nonspecific and might incorrectly be attributed to other processes, especially in ill hospitalized patients. Moreover, patients may have other issues affecting their mental status or their ability to communicate and may require a heightened vigilance for the symptoms of hypoglycemia and strategies to avoid inducing hypoglycemia. For these reasons, targets for glucose, in general, should not be as low as they are in the outpatient setting. A reasonable lower range for preprandial glucose levels is 110 to 120 mg/dL.

Conversely, acute hyperglycemia has a number of detrimental physiologic effects. Mild hyperglycemia is virtually asymptomatic, with early signs being polyuria and polydipsia. In most instances, mild hyperglycemia has no detectable clinical effects over the short term. Severe hyperglycemia, however, can lead to hyperosmolar states and occasionally is a precursor to diabetic ketoacidosis, both of which can have devastating consequences. Glucose levels greater than 200 mg/dL have been demonstrated to have an inhibitory effect on leukocyte function, and clinical trials have shown increases in wound infection and decreased wound strength at and above this level of hyperglycemia [5,6]. Coincidentally, 200 mg/dL is also approximately the renal threshold for glucose filtering. Glycosuria and osmotic diuretic losses of sodium, potassium, and water begin at this level of hyperglycemia. In order to minimize fluid shifts, optimize immune function, and prevent acid-base and electrolyte disturbances, it is reasonable to use a glucose level of 200 mg/dL as the upper limit. Therefore, in order to minimize hypoglycemic events with their more severe consequences and still maintain metabolic balance, a reasonable target range for preprandial glucose in most hospitalized patients is 120 to 200 mg/dL.

In order to achieve this target, one needs to consider myriad clinical factors. Type of diabetes, outpatient medical regimen, antecedent glycemic control, and the duration that the patient will be NPO all impact the management strategy. Additional factors that should be considered are the patient’s acute and chronic nutritional state, comorbid illnesses (especially renal or hepatic dysfunction), and physiologic stress of the illness leading to hospitalization. Moreover, the extent of any planned procedures and type of medical therapies (eg, effects of glucocorticosteroids for example) impact a patient’s glucose metabolism.

Clinical studies have demonstrated that the patients most at risk for hypoglycemia include those with renal insufficiency, those who are chronically malnourished, and those with hypoalbuminemia [7]. Clinical risk factors for hyperglycemia during hospitalization include elevated glucose on admission, higher APACHE III scores, history of multiple diabetic complications, and glucocorticosteroid therapy [4].

NPO and Use of Glucose-Lowering Agents
In general, sulfonylureas should be held whenever a patient is NPO (Table 1). Sulfonylureas have a delayed peak onset (hours) and a long half-life (1 hour > 24 hours) and therefore can lead to hypoglycemia hours after the dose is ingested, especially in patients with decreased caloric intake. Metformin, a biguanide that works by several pathways to improve glycemic control, should also be held in patients who are NPO [8]. Although it is quite uncommon for metformin to cause hypoglycemia, hypoglycemia has been reported in patients with minimal caloric intake and decreasing renal function with metformin use [8]. Therefore, it is safer to withhold the medication when a patient is NPO, particularly if a contrast study is planned (see below).

This patient is also taking insulin glargine, which is a designed insulin that is slowly released from the subcutaneous injection site, providing a continuous low level of insulin with no defined peak and nearly 24 hours of action [9,10] (Table 2). Although it is a new medication, clinical experience with insulin glargine is expanding. In patients with type 2 diabetes, diabetic ketoacidosis is uncommon and thus it may be reasonable to hold insulin glargine for the brief period that the patient is NPO. In this case, however, the patient is taking 2 other agents and is likely to develop significant hyperglycemia if all 3 agents are withheld. It is best to give a portion of the insulin glargine dose to maintain at least a low level of exogenous insulin. Clinical recommendations for the use of NPH insulin suggest using half the usual dose, and this is a reasonable starting point for insulin.
glargine. Clinical use also suggests that continuing the usual dose with close monitoring is reasonable as there is no peak period of action [9,10]. It is important to note that patients with type 1 diabetes require some exogenous insulin at all times even if they are NPO for an extended period. Insulin is necessary to prevent ketolysis in these patients and should be given even if it requires the addition of glucose administration. The patient should have her glucose levels monitored closely by fingerstick at least 4 times per day and her therapy should be tailored based on those levels. The use of short-acting sliding-scale insulin coverage is controversial. Most endocrinologists agree that it is not the ideal method by which to manage diabetic patients, as one is dosing insulin based on retrospective data rather than attempting to anticipate upcoming insulin requirements. Sliding scales are commonly used, however, because of their relative simplicity.

Two prospective trials have shown that sliding-scale insulin therapy alone is not effective at minimizing hyperglycemia [4,11]. A trial in patients with diabetic ketoacidosis showed that length of stay and glycemic control was improved significantly with standing insulin dosing when compared with sliding-scale insulin [11]. More relevant to this case, a prospective trial of diabetic patients admitted with nondiabetic illness showed that patients treated with no glucose-lowering therapy had less hyperglycemia than those treated with sliding-scale insulin. Moreover, standing glucose-lowering therapy (insulin or oral medication) combined with sliding-scale insulin did no better than standing glucose-lowering therapy alone [4]. Based on these data and consensus guidelines, we recommend treating this patient with some standing dose insulin and attempting to anticipate her insulin requirements based on caloric intake and glucose monitoring. If one uses a sliding scale it should be designed with the goal of avoiding hypoglycemia and severe hyperglycemia rather than achieving “tight” control.

Her metformin should be held because of the slight risk for hypoglycemia previously mentioned but also because metformin carries a risk of lactic acidosis, especially in the setting of renal insufficiency. In general, metformin can be given safely to patients with normal renal function. But if acute decreases in renal function are likely or possible, the medication should be held. Patients who have or are at significant risk of hypoperfusion of any etiology (infection, decompensated heart failure, advanced liver disease, or hypovolemia) should not receive metformin [8], as it is likely to accumulate with decreased renal perfusion and increase the risk of lactic acidosis.

Similarly, metformin should be withheld for 48 hours around the time of contrast studies because of the risk of contrast-mediated reduction in renal function and consequent risk of lactic acidosis. Metformin should be held for at least 48 hours after cardiac catheterization, and renal function should be measured and be normal before reinstating this drug [8]. Although it is beyond the scope of this article, there is increasing evidence for the renal protective effects of prophylactic N-acetylcysteine given prior to contrast administration [12].

**Table 1. Oral Glucose-Lowering Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Duration of Action</th>
<th>Metabolism</th>
<th>Use When NPO?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Insulin secretagogues</td>
<td>Varies by drug but generally hours to days</td>
<td>Significant renal clearance, needs dose reduction or discontinuation in renal insufficiency</td>
<td>Hold</td>
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<tr>
<td>Glipizide (Glucotrol)</td>
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<td>Glyburide (Diabeta)</td>
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<td>Glimepriride (Amaryl)</td>
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<td>Biguanides</td>
<td>Not fully known, increases glucose utilization in presence of insulin</td>
<td>Serum T_{1/2} approx 6 hr; drug action is days</td>
<td>Significant renal clearance, contraindicated in renal insufficiency due to risk of lactic acidosis</td>
<td>Hold</td>
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<tr>
<td>Metformin (Glucophage)</td>
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<tr>
<td>Thiazolidinedones</td>
<td>Insulin sensitizers</td>
<td>Drug action is days</td>
<td>Primarily hepatic, dose adjustment in renal insufficiency not necessary</td>
<td>Hold</td>
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<tr>
<td>Rosiglitazone (Avandia)</td>
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<tr>
<td>Pioglitazone (Actos)</td>
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<tr>
<td>Meglitinides</td>
<td>Insulin secretagogues different from sulfonylureas</td>
<td>Short—minutes to hours</td>
<td>Mostly hepatic clearance, dose adjustment in renal insufficiency not necessary</td>
<td>Hold</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
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<tr>
<td>Nateglinide (Starlix)</td>
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<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Inhibit intestinal absorption of carbohydrate</td>
<td>Short—minutes to hours</td>
<td>Renally cleared, dose adjustment in renal insufficiency not clear as drug acts locally in gut</td>
<td>Hold (not effective while NPO)</td>
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<tr>
<td>Acarbose (Precose)</td>
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<td>Miglitol (Glyset)</td>
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Other Medications

Her other medications should be reviewed and evaluated as well. Hospitalization is an opportunity to review the overall care of diabetic patients and ensure the medical regimen is appropriate and effective. The patient has clear indications for angiotensin-converting enzyme (ACE) inhibitor therapy, in consideration of her diabetes, hypertension, and microalbuminuria [13]. She warrants excellent lipid control and meets criteria for HMG-CoA reductase inhibitor therapy [14]. Diltiazem is an effective blood pressure medication and can be continued during hospitalization. All of these medications can be continued. One needs to be aware of the renal hemodynamic effects of ACE inhibitors and therefore minimize the risk of volume depletion and the use of other vasoactive medications. Additionally, one must be aware that the addition of a β-blocker may require the discontinuation of the diltiazem [15].

Cardiac Catheterization

The patient undergoes cardiac catheterization and a single-vessel intracoronary stent is placed. Four hours after the procedure, she is fully alert and hungry and is requesting lunch. Fingerstick glucose levels were 115 mg/dL in early morning and 165 mg/dL at noon.

- Which medicines should be started or reintroduced at this point?

The reintroduction of glucose-lowering agents depends on several factors. Foremost is assessment of the patient’s ability to take in and digest a normal diet and whether further periods of NPO are anticipated. In general, sulfonylureas and other oral glucose-lowering agents should not be restarted at the full dose until the patient is alert, has a good appetite, is eating without vomiting, and no further invasive testing is planned. In this patient’s case, glipizide can safely be restarted on her usual schedule and her insulin glargine can be returned to her usual dose.

Her metformin should be withheld for 48 hours as discussed previously. If there are no contraindications, she should be started on aspirin as a long-term medication because of proven benefit as secondary prevention of cardiac events [16,17]. She should also be taking a β blocker because the cardioprotective benefits of β blockers in patients with unstable coronary syndromes and coronary artery disease are significant [15,18]. The use of β blockers should be undertaken with some care. β Blockers decrease epinephrine release, which in turn diminishes a native pathway for glucose production and raising blood glucose levels, thereby facilitating hypoglycemia. β Blockers can lower the glycemic level for the detection hypoglycemic symptoms [19]. With patient education and monitoring, the benefits of β blockers in this clinical setting outweigh these risks.

CASE 2
Initial Presentation

A 72-year-old man with type 2 diabetes, hypertension, and stable exertional angina presents with new-onset dysarthria and left arm and leg weakness. The patient has chronic difficulty controlling his glucose. His fasting glucose levels range from 180 to 220 mg/dL and his most recent HbA1c was 10%. His medications at home include aspirin, atenolol, lisinopril, terazosin, rosiglitazone, and glyburide. He has a blood pressure of 150/90 mm Hg, and a heart rate of 65 bpm. Height is 178 cm and weight is 120 kg (body mass index, 38). He has fluent but dysarthric speech, decreased gag reflex, a left facial drop, and decreased power in his left upper and lower extremities. A computed tomography scan reveals a right middle cerebral artery territory ischemic infarct. His admission glucose is 280 mg/dL and his creatinine is 1.4 mg/dL.

- What level of glycemic control is appropriate in this patient?

This patient has a large vascular territory ischemic stroke with a background history of poorly controlled diabetes.
and hypertension. He has hyperglycemia at the time of presentation.

Nonlacunar stroke is one of several clinical settings in which strict glycemic control may affect patient outcomes [20]. Multiple studies have demonstrated that hyperglycemia at the time of admission with an acute stroke is a poor prognostic indicator [21,22]. Subgroup analysis from large thrombolysis trials show that patients with hyperglycemia at the time of enrollment in the trial have poorer scores on several scales of neurologic function at 3-month follow-up than patients with euglycemia [20]. Some trials have shown an increased risk for hemorrhagic transformation of ischemic strokes in patients with hyperglycemia. It has not, however, been proven whether hyperglycemia is a causative factor in stroke outcomes or is a marker of more severe strokes and higher stress-mediated hyperglycemia [20]. There are animal models that suggest that hyperglycemia worsens brain edema and cellular function in ischemic strokes and that treatment of hyperglycemia with insulin lessens the extent of neurologic damage [23].

Clinical trials of intensive insulin therapy in acute stroke hopefully will provide further guidance for the acute management of glycemic control in the setting of acute stroke. A trial in diabetic patients with acute myocardial infarction [24,25] has been performed. In the DIGAMI trial, diabetic patients were randomized to intensive insulin therapy (glucose and insulin infusion for the first 24 hours and subcutaneous insulin 4 times per day for 3 months) or standard insulin therapy. The patients in the intensive insulin therapy group had significantly lower 1-year and 3-year mortality [25]. Patients who had no prior use of insulin and low cardiovascular risk received the greatest benefit, with a 58% reduction in in-hospital mortality. Although much of the benefit noted at 1- and 3-year follow-up may have been from improved glycemic control over months, there appears to be benefit in acutely controlling glucose in patients with diabetes mellitus and acute myocardial infarction. The insulin-glucose protocol was designed to keep glucose levels at less than 195 mg/dL [25].

Recent clinical trial data reveal that intensive insulin therapy in critically ill patients provides a survival benefit. Among critically ill patients requiring mechanical ventilation, maintaining glucose levels between 80 to 110 mg/dL improved 30-day survival when prospectively compared with patients maintained in the 180- to 200-mg/dL range [25]. This intensive insulin therapy led to a 34% decrease in inhospital mortality for this cohort of surgical intensive care unit patients. The benefit was greatest in the patients who were the most ill (multiorgan dysfunction, infection with septic shock) [26].

For the patient in case 2, the data are suggestive but not definitive that he would benefit from excellent glucose control [22]. His hyperglycemia on presentation with a large stroke is a negative prognostic indicator. It is therefore appropriate to attempt to aggressively lower his glucose and monitor him closely. His poor glycemic control as an outpatient with oral glucose-lowering therapy indicates that he will likely require insulin therapy. Although making numerous changes in medication regimens in hospitalized patients carries the risk of increased adverse drug reactions after discharge, some changes are strongly indicated and should be made with detailed education of the patient.

- How should his medications be managed?

This patient is going to remain NPO because of risk for aspiration, and both of his oral glucose-lowering medications should be withheld as discussed above. Rosiglitazone is an insulin sensitizer; it should be withheld to lower the risk of hypoglycemia and to simplify the initiation of an insulin regimen. This patient’s sulfonylurea should be discontinued as well.

Intravenous insulin provides the quickest method by which to acutely lower blood glucose and the best method to tightly control it. Some clinical scenarios clearly warrant intravenous insulin. Care of patients with type 1 diabetes with signs of ketoacidosis is an obvious one. Additionally, there are data to support intravenous insulin over subcutaneous insulin in patients with type 1 diabetes who are having a major procedure with general anesthesia [27], particularly intraoperatively and in the early postoperative period. Moreover, type 1 diabetes patients and some type 2 patients who are seriously ill and will be NPO for a prolonged period may have better outcomes with intravenous insulin [2]. Standardized regimens, such as the Portland protocol, have been developed for the use of intravenous insulin [9].

When using intravenous insulin to acutely lower glucose but not to control ketoacidosis, an additional aim is to transition to subcutaneous insulin with a regimen that will maintain glycemic control. After several hours of intravenous dosing and monitoring, the physician can approximate the patient’s total daily insulin requirements. One must be aware, however, that it requires larger doses of insulin to lower blood glucose than to maintain a stable level. Intravenous insulin therapy requires frequent blood glucose monitoring and nursing expertise that often can only be provided in intensive care units or special wards. These are factors that limit its practical application. In the right setting and with attention to detail, one can use short-acting subcutaneous insulin in a similar manner with the same goal of lowering glucose to a target range and transitioning to a longer-acting insulin regimen.

For this patient, an appropriate approach would be to use a dose of subcutaneous intermediate-acting insulin (eg, 10 U
NPH insulin) and to use subcutaneous regular insulin every 2 to 4 hours with dose adjustments based on blood glucose levels. Over 12 to 24 hours, one can estimate the patient's total daily insulin requirements and plan to transition to a twice per day intermediate-acting insulin or a once per day long-acting insulin regimen. We know from this patient's weight and baseline glucose levels that he is likely to require at least 28 U per day. With close monitoring, one can aim for glucose levels in the 100 to 150 mg/dL range. Again, sliding-scale insulin therapy without standing dose insulin and without a plan to anticipate insulin requirements is less effective.

Insulin Therapy and Monitoring

The patient's glucose is monitored every 2 hours. 22 U of regular insulin over 8 hours are required to achieve a glucose level of less than 160 mg/dL. He continues with glucose monitoring and is given supplemental short-acting regular insulin when his glucose levels are greater than 150 mg/dL. He is also given 10 U NPH insulin subcutaneously at 7 AM the day after admission. He does well neurologically and is transitioned to NPH insulin 10 U subcutaneously every 12 hours; during this transition his glucose levels remain 100 to 160 mg/dL. His highest blood pressure is 160/90 mm Hg. He is evaluated by speech therapy and it is determined that with some precautions he can eat a thickened liquid and soft solid diet.

• Which oral medicines should be started at this point?

Reintroduction of oral glucose-lowering agents was discussed above. For this patient with poor control on oral agents prior to hospitalization and good control on NPH insulin, one should encourage the patient to make the switch to long-term insulin therapy. For simplicity's sake, insulin alone should be the starting regimen for this patient. As the patient's caloric intake increases, one can anticipate that his insulin requirements will increase. If his appetite is good and intake fairly consistent, one should add a short-acting insulin before meals. Insulin lispro before each meal or regular insulin twice a day is reasonable and baseline glucose levels that he is likely to require at least 28 U per day. With close monitoring, one can aim for glucose levels in the 100 to 150 mg/dL range. Again, sliding-scale insulin therapy without standing dose insulin and without a plan to anticipate insulin requirements is less effective.

Conclusion

Many factors are involved in providing quality care to hospitalized patients with diabetes. There is a body of literature to help guide therapeutic choices, but the key to making management decisions is considering the multiple factors that affect the individual patient and tailoring therapy to the individual circumstance. Targets for glucose control and use or adjustment of medications vary depending on the clinical situation. Moreover, one needs to be prepared to adjust doses of glucose-lowering agents based on monitoring and strive to be proactive and anticipate medication requirements. The overall aim in glycemic control in the hospitalized patient with diabetes is to lower glucose to a level that optimizes the patient's outcome without inducing hypoglycemia. This control of glucose levels should be obtained primarily with standing dose glucose-lowering agents. The addition of short-acting sliding-scale insulin should be used only to supplement standing dose regimens and be used to adjust future doses.

References


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