CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will learn the relationship between glycemic control and clinical outcomes in hospitalized medical and surgical patients who are not in an intensive care unit, and outline strategies for achieving glycemic targets in these patients

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How to manage type 2 diabetes in medical and surgical patients in the hospital

ABSTRACT

Many patients admitted to the hospital have diabetes mellitus—diagnosed or undiagnosed—and others develop hyperglycemia from the stress of hospitalization. This paper discusses the prevalence, outcomes, and evidence for best management of hyperglycemia and diabetes in hospitalized patients outside the critical care setting.

KEY POINTS

Hyperglycemia and undiagnosed diabetes are very common in hospitalized patients and are associated with poorer outcomes.

Hospitalized patients should be screened for diabetes with a blood glucose measurement. Those who have a value of 140 mg/dL or higher should be tested for hemoglobin A_{1c}. A value higher than 6.5% is very specific for diabetes, although not very sensitive for it.

Most hospitalized patients with diabetes and elevated blood glucose values (or hyperglycemia) should receive subcutaneous insulin treatment with a basal-bolus regimen or a multidose combination of neutral protamine Hagedorn (NPH) plus regular insulin. Selected patients with severe insulin resistance and persistent hyperglycemia despite subcutaneous insulin may benefit from continuous intravenous insulin infusion.

Sliding-scale insulin as a single form of therapy in patients with diabetes is undesirable.

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HYPERGLYCEMIA AND DIABETES mellitus are very common in hospitalized patients. Although more data are available on the prevalence of this problem and on how to manage it in the intensive care unit (ICU) than on regular hospital floors, the situation is changing. Information is emerging on the prevalence and impact of hyperglycemia and diabetes in the non-ICU setting, which is the focus of this paper.

HYPERGLYCEMIA IS COMMON AND PREDICTS POOR OUTCOMES

Cook et al,[1] in a survey of 126 US hospitals, found that the prevalence of hyperglycemia (blood glucose > 180 mg/dL) was 46% in the ICU and 32% in regular wards.

Kosiborod et al[2] reported that hyperglycemia (blood glucose > 140 mg/dL) was present in 78% of diabetic patients hospitalized with acute coronary syndrome and 26% of similar hospitalized nondiabetic patients.

Hyperglycemia is a common comorbidity in medical-surgical patients in community hospitals. Our group[3] found that, in our hospital, 62% of patients were normoglycemic (ie, had a fasting blood glucose < 126 mg/dL or a random blood glucose < 200 mg/dL on two occasions), 26% had known diabetes, and 12% had new hyperglycemia. Further, new hyperglycemia was associated with a higher in-hospital death rate than the other two conditions.

Failure to identify diabetes is a predictor of rehospitalization. Robbins and Webb[4] reported that 30.6% of those who had diabetes that was missed during hospitalization were readmitted within 30 days, compared with 9.4% of patients with diabetes first diagnosed during hospitalization.

TABLE 1

Categories of diabetes

TEST	NORMAL	PREDIABETES	DIABETES
Hemoglobin A_{1c}	< 5.7%	5.7%–6.4%	≥ 6.5%
Fasting plasma glucose	< 100 mg/dL	100–125 mg/dL	≥ 126 mg/dL
2-Hour plasma glucose [a]	< 140 mg/dL	140–199 mg/dL	≥ 200 mg/dL[b]

[a] Performed during an oral glucose tolerance test [b] Or random plasma glucose ≥ 200 mg/dL plus symptoms

INFORMATION FROM AMERICAN DIABETES ASSOCIATION. DIAGNOSIS AND CLASSIFICATION OF DIABETES MELLITUS. DIABETES CARE 2010; 33(SUPPL 1):S62–S69.

WHAT DIAGNOSTIC CRITERIA SHOULD WE USE?

Blood glucose greater than 140 mg/dL

A consensus statement from the American Association of Clinical Endocrinologists (ACE) and the American Diabetes Association (ADA)[5] defines in-hospital hyperglycemia as a blood glucose level greater than 140 mg/dL on admission or in the hospital. If the blood glucose is higher than this, the question arises as to whether the patient has preexisting diabetes or has stress hyperglycemia.

Hemoglobin A_{1c} is not very good by itself as a screening test, but is very specific as a follow-up test

Hemoglobin A_{1c} of 6.5% or higher

In view of the uncertainty as to whether a patient with an elevated blood glucose level has preexisting diabetes or stress hyperglycemia, upcoming guidelines will recommend measuring the hemoglobin A_{1c} level if the blood glucose level is higher than 140 mg/dL.

A patient with an elevated blood glucose level (>140 mg/dL) whose hemoglobin A_{1c} level is 6.5% or higher can be identified as having diabetes that preceded the hospitalization. Hemoglobin A_{1c} testing can also be useful to assess glycemic control before admission and in designing an optional regimen at the time of discharge. In patients with newly recognized hyperglycemia, a hemoglobin A_{1c} measurement can help differentiate patients with previously undiagnosed diabetes from those with stress-induced hyperglycemia.

Clinicians should keep in mind that a hemoglobin A_{1c} cutoff of 6.5% identifies fewer cases of undiagnosed diabetes than does a high fasting glucose concentration, and that a level less than 6.5% does not rule out the diagnosis of diabetes. Several epidemiologic studies[6] have reported a low sensitivity (44% to 66%) but a high specificity (76% to 99%) for hemoglobin A_{1c} values higher than 6.5% in an outpatient population. The high specificity therefore supports the use of hemoglobin A_{1c} to confirm the diagnosis of diabetes in patients with hyperglycemia, but the low sensitivity indicates that this test should not be used for universal screening in the hospital.

Many factors can influence the hemoglobin A_{1c} level, such as anemia, iron deficiency, blood transfusions, hemolytic anemia, and renal failure.

Until now, if patients had hyperglycemia but no prior diagnosis of diabetes, the recommendation was for an oral 2-hour glucose tolerance test shortly after discharge to confirm the diagnosis of diabetes. Norhammar et al[7] performed oral glucose tolerance tests in patients admitted with acute myocardial infarction, and Matz et al[8] performed glucose tolerance tests in patients with acute stroke. They found that impaired glucose tolerance and undiagnosed type 2 diabetes were very common in these two groups. However, physicians rarely order oral glucose tolerance tests. We believe that hemoglobin A_{1c} will be a better tool than an oral glucose tolerance test to confirm diabetes in hyperglycemic patients in the hospital setting.

In its January 2010 recommendations,[9] the ADA lists criteria for the categories of normal, prediabetes, and diabetes, based on fasting and 2-hour postprandial plasma glucose levels and hemoglobin A_{1c} (TABLE 1).

WHAT IS THE ASSOCIATION BETWEEN HYPERGLYCEMIA AND OUTCOMES?

In 2,471 patients admitted to the hospital with community-acquired pneumonia, McAlister et al[10] found that the rates of hospital complications and of death rose with blood glucose levels.

Falguera et al[11] found that, in 660 episodes of community-acquired pneumonia, the rates of hospitalization, death, pleural effusion, and concomitant illnesses were all significantly higher in diabetic patients than in nondiabetic patients.

Noordzij et al[12] performed a case-control study of 108,593 patients who underwent noncardiac surgery. The odds ratio for perioperative death was 1.19 (95% confidence interval [CI] 1.1–1.3) for every 1-mmol/L increase in the glucose level.

Frisch et al,[13] in patients undergoing noncardiac surgery, found that the 30-day rates of death and of in-hospital complications were all higher in patients with diabetes than without diabetes.

Our group[3] identified hyperglycemia as an independent marker of in-hospital death in patients with undiagnosed diabetes. The rates of death were 1.7% in those with normoglycemia, 3.0% in those with known diabetes, and 16.0% ($P < .01$) in those with new hyperglycemia.

The ACE/ADA consensus panel[14] set the following glucose targets for patients in the non-ICU setting:

- Pre-meal blood glucose < 140 mg/dL
- Random blood glucose < 180 mg/dL.

On the other hand, hypoglycemia is also associated with adverse outcomes. Therefore, to avoid hypoglycemia, the insulin regimen should be reassessed if blood glucose levels fall below 100 mg/dL. New guidelines will suggest keeping the blood glucose between 100 and 140 mg/dL.

HOW SHOULD WE MANAGE HYPERGLYCEMIA IN THE NON-ICU SETTING?

The ACE/ADA guidelines recommend subcutaneous insulin therapy for most medical-surgical patients with diabetes, reserving intravenous insulin therapy for hyperglycemic crises and uncontrolled hyperglycemia.[14]

Oral antidiabetic agents are not generally recommended, as we have no data to support their use in the hospital. Another argument against using noninsulin therapies in the hospital is that sulfonylureas, especially glyburide (Diabeta, Micronase) are a major cause of hypoglycemia. Metformin (Glucophage) is contraindicated in decreased renal function, in hemodynamic instability, in surgical patients, and with the use of iodinated contrast dye. Thiazolidinediones are associated with edema and congestive heart failure, and they take up to 12 weeks to lower blood glucose levels. Alpha-glucosidase inhibitors are weak glucose-lowering agents. Also, therapies directed at glucagon-like-protein 1 can cause nausea and have a greater effect on postprandial glucose.[14]

The two main options for managing hyperglycemia and diabetes in the non-ICU setting are short-acting insulin on a sliding scale and basal-bolus therapy, the latter with either NPH plus regular insulin or long-acting plus rapid-acting insulin analogues.

Basal-bolus vs sliding scale insulin: The RABBIT-2 trial

In the RABBIT 2 trial (Randomized Basal Bolus Versus Sliding Scale Regular Insulin in Patients With Type 2 Diabetes Mellitus),[15] our group compared the efficacy and safety of a basal-bolus regimen and a sliding-scale regimen in 130 hospitalized patients with type 2 diabetes treated with diet, with oral hypoglycemic agents, or with both. Oral antidiabetic drugs were discontinued on admission, and patients were randomized to one of the treatment groups.

Reassess the insulin regimen if blood glucose levels fall below 100 mg/dL

In the basal-bolus group, the starting total daily dose was 0.4 U/kg/day if the blood glucose level on admission was between 140 and 200 mg/dL, or 0.5 U/kg/day if the glucose level was between 201 and 400 mg/dL. Half of the total daily dose was given as insulin glargine (Lantus) once daily, and the other half was given as insulin glulisine (Apidra) before meals. These doses were adjusted if the patient's fasting or pre-meal blood glucose levels rose above 140 mg/dL or fell below 70 mg/dL.

The sliding-scale group received regular insulin four times daily (before meals and at

bedtime) for glucose levels higher than 140 mg/dL; the higher the level, the more they got.

The basal-bolus regimen was better than sliding-scale regular insulin. At admission, the mean glucose values and hemoglobin A_{1c} values were similar in both groups, but the mean glucose level on therapy was significantly lower in the basal-bolus group than in the sliding-scale group, 166 ± 32 mg/dL vs 193 ± 54 mg/dL, $P < .001$). About two-thirds of the basal-bolus group achieved a blood glucose target of less than 140 mg/dL, compared with only about one-third of the sliding-scale group. The basal-bolus group received more insulin, a mean of 42 units per day vs 12.5 units per day in the sliding-scale group. Yet the incidence of hypoglycemia was 3% in both groups.

NPH plus regular vs detemir plus aspart: The DEAN trial

Several long-acting insulin analogues are available and have a longer duration of action than NPH. Similarly, several newer rapid-acting analogues act more rapidly than regular insulin. Do these pharmacokinetic advantages matter? And do they justify the higher costs of the newer agents?

Oral antidiabetic agents are not generally recommended in the hospital

In the randomized Insulin Detemir Versus NPH Insulin in Hospitalized Patients With Diabetes (DEAN) trial,[16] we compared two regimens: detemir plus aspart in a basal-bolus regimen, and NPH plus regular insulin in two divided doses, two-thirds of the total daily dose in the morning before breakfast and one-third before dinner, both doses in a ratio of two-thirds NPH and one-third regular, mixed in the same syringe. We recruited 130 patients with type 2 diabetes mellitus who were on oral hypoglycemic agents or insulin therapy.

NPH plus regular was just as good as detemir plus aspart in improving glycemic control. Blood glucose levels fell during the first day of therapy and were similar in both groups throughout the trial, as measured before breakfast, lunch, and dinner and at bedtime. The mean total daily insulin dose was not significantly different between treatment groups: 56 ± 45 units in the basal-bolus detemir-aspart group and 45 ± 32 units in the NPH-regular group. However, the basal-bolus group received significantly more short-acting insulin: 27 ± 20 units a day of aspart vs 18 ± 14 units of regular.

Somewhat fewer patients in the NPH-regular group had episodes of hypoglycemia, although the difference between groups was not statistically significant.

In a univariate analysis of the RABBIT-2 and DEAN trials,[17] factors that predicted a blood glucose level less than 60 mg/dL were older age, lower body weight, higher serum creatinine level, and previous insulin therapy. Factors that were not predictive were the hemoglobin A_{1c} level and the enrollment blood glucose level. Based on these data, we believe that to reduce the rate of hypoglycemia, lower insulin doses are needed in elderly patients and patients with renal impairment, and that if patients have been taking insulin before they come to the hospital, the dose should be cut back by about 25% while they are hospitalized.

Basal-bolus vs sliding-scale insulin for surgical patients: The RABBIT 2 Surgery trial

Does better glucose control in surgical patients affect outcomes in patients undergoing general surgery? To find out, we performed a prospective, multicenter, randomized, open-label trial in general surgery patients not in the ICU.[18] We recruited and randomized 211 patients with type 2 diabetes who were on diet therapy or oral hypoglycemic agents or insulin in low doses (< 0.4 U/kg/day).

Oral drugs were discontinued on admission, and patients were randomized to receive either a basal-bolus regimen of glargine plus glulisine or regular insulin on a sliding scale. The basal-bolus group got 0.5 U/kg/day, half of it as glargine once daily and half as glulisine before meals. The total daily dose was reduced to 0.3 U/kg/day in patients age 70 and older or who had a serum creatinine level of 2.0 mg/dL or higher.

The goal was to maintain fasting and premeal glucose concentrations between 100 and 140 mg/dL. The total daily dose was raised by 10% (mostly in the glargine dose) if the blood glucose level was in the range of 141 to 180 mg/dL, and by 20% if the glucose level was higher than 181 mg/dL. The dose was decreased by 10% for glucose levels between 70 and 99 mg/dL, was decreased by 20% if the

glucose level was between 40 and 69, and was held if the glucose level was lower than 40 mg/dL. If a patient was not able to eat, insulin glulisine was held until meals were resumed.

The sliding-scale group received regular insulin four times a day for blood glucose levels higher than 140 mg/dL.

The primary outcomes measured were the difference between groups in mean daily blood glucose concentration and a composite of hospital complications including postoperative wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. Secondary outcomes were differences between groups in mean fasting and pre-meal blood glucose, number of hypoglycemic episodes (blood glucose < 70 mg/dL), hyperglycemic episodes (blood glucose > 200 mg/dL), length of hospital stay, need for intensive care, and rate of complications including wound infection, pneumonia, acute renal failure, and death.

Blood glucose levels were significantly lower in the basal-bolus group through the first 7 days after randomization, as measured before breakfast, lunch, and dinner, and at bedtime, and then they converged.

More patients in the sliding-scale group had hospital complications, 26 vs 9, $P = .003$. On the other hand, more patients in the basal-bolus group had episodes of hypoglycemia: 24 (23%) vs 5 (4.7%) had episodes of less than 70 mg/dL ($P < .001$), 12 (12%) vs 2 (1.9%) had episodes of less than 60 mg/dL ($P = .005$), and 4 (3.8%) vs 0 had episodes of less than 40 mg/dL ($P = .057$). The mean total daily dose of insulin was 33.4 units in the basal-bolus group and 12.3 units in the sliding-scale group.

WHAT HAVE WE LEARNED?

Don't use a sliding-scale regimen as a single agent in patients with diabetes. Glycemic control is better with a basal-bolus regimen than with a sliding-scale regimen, and a basal-bolus insulin regimen is preferred for most patients with hyperglycemia.

The old human insulins (ie, regular and NPH) are still good and improve glycemic control as well as the new basal insulin analogues (detemir and aspart) do.

Improved control may reduce the rate of hospital complications, according to preliminary evidence. More studies are under way.

One size does not fit all. Those who are elderly or who have impaired renal function should receive lower doses of insulin, eg, 0.3 U/kg/day instead of 0.5 U/kg/day. Those who are on insulin should have their dose decreased when they are admitted to the hospital. Perhaps lean patients with type 2 diabetes should also have a lower dose.

Most hospitalized patients with diabetes and elevated blood glucose values (or hyperglycemia) should receive subcutaneous insulin treatment with a basal-bolus regimen or a multidose combination of NPH plus regular insulin. Selected patients with severe insulin resistance and persistent hyperglycemia despite subcutaneous insulin may benefit from continuous intravenous insulin infusion.

Patients treated with insulin at home should continue to receive insulin therapy in the hospital. However, the insulin dosage should be reduced by about 25% to allow for lower food intake.

QUESTIONS FOR FURTHER STUDY

Should we modify the standard basal-bolus regimen?

In a typical basal-bolus regimen, patients get 50% of their total daily insulin dose in the form of a basal injection and 50% in the form of rapid-acting boluses before meals. However, for a variety of reasons, hospitalized patients do not eat very much. Thus, a 50-50 basal-bolus regimen may not be ideal for patients with poor oral intake.

NPH plus regular insulin was just as good as detemir plus aspart in improving glycemic control

In the Basal-PLUS trial, currently under way, we are comparing the safety and efficacy of a daily dose of basal insulin (glargine) plus correction doses of a rapid-acting insulin analogue (glulisine) on a sliding scale and a standard basal-bolus regimen in medical and surgical patients.

Does one glycemic target fit all patients?

Falciglia et al[19] found an association between hyperglycemia and death in patients with unstable angina, arrhythmias, stroke, pneumonia, gastrointestinal bleeding, respiratory failure, sepsis, acute renal failure, and congestive heart failure. However, they found no such association in patients with chronic obstruc-

tive pulmonary disease, liver failure, diabetic ketoacidosis, gastrointestinal neoplasm, musculoskeletal disease, peripheral vascular disease with bypass, hip fracture, amputation due to peripheral vascular disease, or prostate surgery. Should patients in this second group be treated with a less-intensive insulin regimen?

What is the best regimen after hospital discharge?

We are conducting a prospective clinical trial to assess the impact of insulin after hospital discharge. Our current practice when a patient is discharged from the hospital is as follows:

- If the admission hemoglobin A_{1c} level is less than 7%, we restart the previous outpatient treatment regimen of oral antidiabetic agents, or insulin, or both.
- If the admission hemoglobin A_{1c} is between 7% and 9%, we restart the outpatient oral agents and continue glargine once daily at 50% to 80% of the hospital dose.
- If the hemoglobin A_{1c} level is higher than 9%, we discharge the patient on a basal-bolus regimen at the same dosage as in the hospital. As an alternative, we could restart the oral agents and add glargine once daily at 80% of the hospital dose. ■

More patients in the sliding-scale group than in the basal-bolus group had hospital complications

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