American College of Endocrinology
Position Statement on Inpatient Diabetes and Metabolic Control*

*By the American College of Endocrinology Task Force on Inpatient Diabetes and Metabolic Control.
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ACE Position Statement

INTRODUCTION

Diabetes is the fourth most common comorbid condition complicating all hospital discharges. In 1997, diabetes was present in 9.5% of all hospital discharges and 29% of patients undergoing cardiac surgery. Diabetes causes a twofold to fourfold increase in rates of hospitalizations and increases hospital length of stay by 1 to 3 days, depending on the admitting diagnosis. Furthermore, recent studies clearly show that hyperglycemia in hospitalized patients complicates numerous illnesses and is an independent risk factor for adverse outcomes.

Although multiple organizations have issued numerous guidelines for the outpatient management of diabetes, no such guidelines have been formulated for inpatient management. As the result of recent clinical trials and focused research efforts, it is now apparent that new approaches and intensified efforts at metabolic regulation may improve short-, intermediate-, and long-term outcomes in patients with diabetes in the hospital for therapeutic procedures or for treatment of the complications of this illness.

For this reason, we have come together as a critical consensus panel to review this research with the investigators performing that research, to formulate standards for diabetes management in the hospital, and to suggest techniques by which these goals and targets may be achieved. To guide us in our considerations, the following questions were addressed:

1. **What evidence exists that in-hospital hyperglycemia is associated with adverse outcomes?**

In-hospital morbidity and mortality are increased by hyperglycemia in many different medical and surgical conditions:

- Meta-analysis of 15 studies reported that hyperglycemia (blood glucose >110 mg/dL [6.1 mmol/L]) with or without a prior diagnosis of diabetes increased both in-hospital mortality and congestive heart failure (CHF) in patients admitted for acute myocardial infarction (1). Similar data were reported in a prospective study of 336 patients (2).
- Hyperglycemia (fasting blood glucose >126 mg/dL [7.0 mmol/L], random blood glucose >200 mg/dL [11.1 mmol/L]) on general medical and surgical units was associated with an 18-fold increase in in-hospital mortality, a longer length of stay (9 vs. 4.5 days), more subsequent nursing home care, and a greater risk of infection (3).

- Hyperglycemic patients undergoing cardiac surgery suffer greater mortality, increased deep-wound infections, and more overall infection (4,5). In fact, hyperglycemia, on the first and second postoperative days, was the single most important predictor of serious infectious complications.
- In patients treated for critical illness, it was noted that hyperglycemic patients treated with conventional therapy suffer increased overall mortality and an increased risk of sepsis, acute renal failure, and critical illness-related neuropathy (6).
- In 1,826 intensive care unit (ICU) patients, mortality was directly correlated with increasing glucose levels above 80 mg/dL (4.4 mmol/L), showing a direct and proportional correlation (7).
- Both diabetes and hyperglycemia have been associated with a poor outcome in patients with cerebrovascular accidents. A meta-analysis of 26 studies on stroke showed increased in-hospital mortality in patients with blood glucose levels of 110 to 126 mg/dL (6.1-7 mmol/L) (8). Furthermore, stroke survivors with a blood glucose of 121 to 144 mg/dL (6.7-8 mmol/L) without known diabetes showed worse functional recovery. Patients with known diabetes and/or newly discovered hyperglycemia (blood glucose 140 mg/dL [7.8 mmol/L]) had more severe strokes with greater mortality (9).
- It is well known that pregnancy complicated by uncontrolled diabetes results in poor fetal outcomes, but it is less well known that intensive glycemic control during labor and delivery also significantly benefits fetal well-being (10).

2. **Does reduction of hyperglycemia improve outcomes?**

Elimination of hyperglycemia with intravenous infusions of insulin in the ICU reduces morbidity and mortality in acutely ill patients. In ICU patients treated for hyperglycemia (>110 mg/dL [6.1 mmol/L]) with intensive intravenous insulin infusions, hospital mortality was reduced by 34% in a randomized prospective trial (6). Hyperglycemic cardiac surgery patients treated with intravenous insulin infusions used for the first 3 postoperative days demonstrated reductions in absolute and risk-adjusted mortality of 57% and 50%, respectively (11). Conversely, increasing hyperglycemia was shown to have a direct relationship with, and is an independent risk factor for, death after coronary bypass surgery (11). Long-term survival rates in diabetic patients with acute myocardial infarction were improved by 28% at 3.4 years when

treated in a randomized prospective trial with insulin infusions designed to achieve normoglycemia at the time of infarct (12).

In addition to reductions in hospital mortality, reductions in infection rates, intubation times, lengths of hospital stay, and costs have also been demonstrated. Deep sternal wound infection rates in cardiac surgery patients are directly correlated with increasing postoperative glucose levels. The rate of this serious complication was reduced by 66%—to a rate equal to that seen in the nondiabetic population—with the use of an intravenous insulin infusion for 3 postoperative days (13). Intensive insulin therapy in ICU patients resulted in decreases in sepsis (46%), acute renal failure (41%), transfusions (50%), and critical illness polyneuropathy (44%) (6).

In the cardiac surgery population, length of hospital stay was reduced by 1 day for each 50 mg/dL lowering of the average 3-day postoperative blood glucose (14). This, along with reductions in infectious complications, more than offset the additional costs of intravenous insulin, resulting in a net savings of more than $680/patient (14).

The cost of intravenous therapy in patients with acute myocardial infarction was $24,000/quality adjusted life-year (QALY). This cost is comparable to other well-accepted medical interventions. These benefits of treating hyperglycemia were independent of a prior diagnosis of diabetes. No current data exist differentiating hyperglycemia in patients with established diabetes compared with hyperglycemia in nondiabetic populations.

3. To what extent does the impact of metabolic regulation extend beyond merely glycemic regulation?

There are 4 distinct effects, separate from reduction of hyperglycemia, that may explain the beneficial effects of insulin in these clinical trials. First, insulin inhibits lipolysis; elevated free fatty acids have been associated with poor outcomes, particularly cardiac arrhythmias. Second, insulin inhibits inflammatory growth factors (activator protein 1 and early growth response gene-1), which are particularly important in acute myocardial infarction. Third, insulin stimulates endothelial nitric oxide synthase, which subsequently enhances nitric oxide, resulting in arterial vasodilation in addition to a variety of other beneficial effects on oxidation and inflammation. Finally, insulin, in the environment of euglycemia or near-euglycemia, appears to inhibit proinflammatory cytokines, adhesion molecules, and chemokines, in addition to acute phase proteins. It may be that one or more of these mechanisms are responsible for the improved outcomes reported with insulin-treated hyperglycemia. Further research will be required to differentiate these mechanisms from the improvement of hyperglycemia per se.

4. What targets should be attained?

As stated earlier, a recent randomized prospective study by Van den Berghe et al (6) demonstrated that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL (6.1 mmol/L) reduces morbidity and mortality among critically ill patients in the surgical ICU. Similar outcomes were found in a randomized ICU trial done in post-myocardial infarction. Furthermore, prospective, observational, nonrandomized trials have shown that decreasing hyperglycemia reduces morbidity and mortality in all patients, regardless of a prior history of diabetes. It is reasonable, therefore, to assume that achievement of near-normal glycemia is beneficial and desirable in all ICU patients with elevated glucose.

The upper limits for glycemic targets shown in Table 1 are intended to provide clinicians with guidelines for promoting improved outcomes, although the targets for non-intensive care patients are supported by data only from prospective observational studies (Table 1).

Values above 180 mg/dL (10 mmol/L) are an indication to monitor glucose levels more frequently to determine the direction of any glucose trend and the need for more intensive intervention. Achieving these targets may require consultation with an endocrinologist or diabetes specialist.

Separate upper-limit targets in pregnancy have been developed to address the increased risk of poor outcomes caused by hyperglycemia in pregnancy (Table 2).

The occurrence of significant hyperglycemia in the hospital requires close follow-up after discharge. In those with previously diagnosed diabetes and an elevated A1C, the preadmission diabetes care plan requires revision. In those without previously diagnosed diabetes, the differentiation between hospital-related hyperglycemia and undiagnosed diabetes requires follow-up testing (fasting blood glucose, 2-hour oral glucose tolerance test) once the patients are metabolically stable according to established criteria.

Table 1
Upper Limits for Glycemic Targets

Intensive care unit	Non-critical care units	
	Preprandial	Maximal glucose
110 mg/dL (6.1 mmol/L)	110 mg/dL (6.1 mmol/L)	180 mg/dL (10.0 mmol/L)

Table 2 Upper Limits for Glycemic Targets in Pregnancy		
Prelabor		Labor and delivery
Preprandial	1-hour postprandial	Labor and delivery
100 mg/dL (5.6 mmol/L)	120 mg/dL (6.7 mmol/L)	100 mg/dL (5.6 mmol/L)

5. What methods for such regulation should be used?

Insulin, given either intravenously as a continuous infusion or subcutaneously, is currently the only available agent for effectively controlling glycemia in the hospital. A number of protocols have been published for continuous intravenous insulin (CII) therapy. These protocols have been shown to be safe and effective in achieving the glucose targets specified in Tables 1 and 2. In most studies, glucose or parenteral nutrition is coadministered, which may increase insulin requirements.

Indications for intravenous insulin therapy include but are not limited to:

- Critical illness
- Prolonged NPO (nothing by mouth) status in patients who are insulin deficient
- Perioperative period
- After organ transplantation
- Total parenteral nutrition therapy
- Elevated glucose exacerbated by high-dose glucocorticoid therapy
- Stroke
- Labor and delivery
- As a dose-finding strategy prior to conversion to subcutaneous (SQ) insulin therapy
- Other illnesses requiring prompt glucose control

In surgical patients discharged from the ICU to lower-acuity units, glucose levels should be maintained as close as possible to euglycemic levels, either by intensive SQ therapy or preferably by continuation of intravenous insulin therapy if at all possible.

For patients not meeting these criteria, a trial of subcutaneous insulin therapy is recommended. A variety of effective protocols are available. Effective insulin therapy must provide both basal and nutritional meal and/or intravenous glucose coverage in order to achieve the target goals. Hospitalized patients often require high insulin doses to achieve desired target glucose levels. In addition to basal and nutritional insulin requirements, patients often require supplemental or correction insulin for treatment of unexpected hyperglycemia. Use of "sliding scale" insulin alone is discouraged; evidence does not support this technique because it has resulted in unacceptably high rates of hyperglycemia, hypoglycemia, and iatrogenic diabetic ketoacidosis in hospitalized patients.

The use of standardized protocols that are developed by multidisciplinary teams is associated with improved glycemic control and lower rates of hypoglycemia. In addition to specifying insulin dose, protocols should also include specific guidelines for identifying patients at risk for hypoglycemia and actions to be taken to prevent and treat hypoglycemia.

Hospital systems should be assessed for safety and quality of care. Adjustments may be required for appropriate provision of diabetes care, including timely delivery of meal trays, point-of-care blood glucose testing, and the administration of diabetes medications. Nursing staff should receive adequate and ongoing in-service training on the specialized needs of the inpatient with diabetes, especially with regard to insulin therapy.

Utilizing the team approach to inpatient care has been shown to reduce length of stay and improve clinical outcomes in patients with diabetes (15,16). In addition to the physician, the team may include specialty staff such as a qualified diabetes educator. Diabetes educators and nursing staff should collaborate in the provision of basic "survival skills" when needed to allow for a safe discharge.

Discharge planning should be initiated well in advance. It should explore community resources and arrange for follow-up comprehensive outpatient diabetes self-management training.

6. What is the molecular basis for improved outcomes?

The results of recent investigations have shown multiple mechanisms by which insulin may favorably alter the metabolic abnormalities seen in the hyperglycemic patient.

Biochemical evidence suggests that the reduction in mortality in critically ill patients with intravenous insulin infusions occurs because of favorable alterations in myocardial and skeletal muscle metabolism (17-19). These alterations down-regulate the paradoxical overutilization of free fatty acids that occurs during the hyperglycemic period and stimulate oxidative glycolysis.

Favorable improvements in cell membrane stability, myocardial contractility, and endothelial function result along with decreases in inflammatory mediators and increases in nitric oxide.

Reduction of infectious complications may occur because of the apparent eradication of nonenzymatic glycosylation of proteins critical to adequate function of the immune system (20-22). These include inactivation of immunoglobulin G, impaired opsin binding of complement, activation of collagenase, and inhibition of neutrophil functions, including delayed chemotaxis, impaired phagocytosis, and hindered bactericidal capability (23-27).

7. What are the needs for future research?

The following are suggested research studies for the future:

- Follow-up studies on hospitalized patients without prior diagnosis of diabetes who develop hyperglycemia, especially those with cardiovascular disease, to determine the percentage of patients who will eventually develop permanent abnormalities of glucose metabolism.
- Additional randomized clinical trials in non-ICU patients to better define the optimal blood glucose levels to prevent the mortality and morbidity of acute illness.
- Studies on the role of abnormal fatty acid metabolism in the hyperglycemia of acute illness.
- Studies to determine the best methodologies and hospital systems for improving glycemic control and clinical outcomes.
- Additional cost-effectiveness studies.
- Studies to investigate further the mechanisms by which insulin exerts its beneficial action.

SUMMARY

Hyperglycemia in hospitalized patients is a common, serious, and costly health care problem with profound medical consequences. Data from multiple studies confirm that hospitalized patients with hyperglycemia suffer significant excess mortality and morbidity, prolonged length of stay, unfavorable postdischarge outcomes, and significant excess health care costs.

Randomized controlled inpatient clinical trials as well as prospective observational and retrospective studies have demonstrated improved outcomes resulting from more aggressive management of hyperglycemia. The American College of Endocrinology, the American Association of Clinical Endocrinologists, and the cosponsoring organizations strongly support the need for early detection of hyperglycemia in the hospital and an aggressive management approach to improve outcomes.

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