Counterpoint: Inpatient Glucose Management

A premature call to arms?

Recently, the attention of the diabetes community has shifted to glycemic management in the inpatient setting, where there has been a rising chorus in support of stricter blood glucose control. We applaud the spirit of the current American College of Endocrinology (ACE) recommendations, which attempt to improve the hospital management of hyperglycemia (1). However, as we examine the very limited evidence upon which these guidelines are based, we are concerned about such prematurely stringent glucose targets. Indeed, there is a paucity of well-controlled randomized trials in which the feasibility and safety of specific insulin strategies in the variety of inpatient settings have been validated. Moreover, few have assessed actual outcomes at different glycemic ranges.

We all recognize that several cross-sectional studies have consistently demonstrated that hyperglycemia correlates with increased morbidity and mortality in the acutely ill, particularly in the critically ill and in the perioperative setting (2–4). This association holds for both patients with previously diagnosed diabetes and those with newly recognized hyperglycemia (5). However, the directionality of this relationship remains controversial. Does acute hyperglycemia lead to poor clinical outcomes or is it a reflection of sicker patients, due to increased counter-regulatory forces that simply manifest their stress in the form of elevated blood glucose? Is an elevated blood glucose a marker or a pathogenic mechanism of disease in these patients?

Experimental evidence has clearly supported a cause-and-effect relationship. Leukocyte action, immunoglobulin production, wound healing, collagen production, endothelial function, cardiac performance, and fluid balance are each impaired in the setting of hyperglycemia, particularly when severe (6,7). Admittedly, most data stem from in vitro observations and from in vivo investigations employing animal models (8–10). Moreover, these studies were typically designed to contrast markedly elevated versus normal ambient glucose concentrations (8–10). And, because insulin has beneficial vascular and anti-inflammatory effects (11), it is even less clear whether hyperglycemia or relative insulin deficiency was the major contributor to the increased risk in the in vivo models.

There have been only two well- regarded randomized clinical trials indicating benefit from short-term strict glucose control in hospitalized patients (12,13). In addition, uncontrolled non-randomized interventional reports in cardiothoracic surgical patients showed improved outcomes with intensive insulin regimens and better glycemic control (14,15). In light of these studies, the ACE sponsored a consensus conference that was cosponsored by several other professional organizations, including the American Diabetes Association (ADA) and the Endocrine Society. Subsequently, the ACE published a position statement (1) with very specific stringent targets for the inpatient management of the hyperglycemic patient. According to the ACE, blood glucose concentrations for intensive care unit (ICU) patients should be maintained at <110 mg/dl. In the noncritically ill, the upper limit for preprandial glucose is 110 mg/dl, with no peak postprandial reading to rise above 180 mg/dl. It is most important to clarify that these recommendations arose specifically from the ACE, not from the ADA or the Endocrine Society. In the case of the ADA, not even a technical review as good and comprehensive as the recent one devoted to the management of hyperglycemia and diabetes in hospitals (16) has the authority to make such critical recommendations. Only the ADA Professional Practice Committee, after rigorously interpreting the evidence and weighing the risk-benefit ratio as well as the burden and societal costs, has the authority to issue the Clinical Practice Recommendations, which are published in Diabetes Care each January.

Given that in most hospitals such targets are a significant departure from the status quo, the recommendations have led to enormous concern among hospital officials and administrators, as they have quickly come to the realization that glucose management has been essentially ignored for decades in most institutions. This increased awareness is clearly a good thing; at the very least, poor glycemic control in the hospital is bad care and probably increases length of stay. At worst, as suggested by these studies, poor glycemic control may worsen short- and perhaps even long-term outcomes. Diabetologists, who have long been frustrated about the care received by their previously well-controlled patients once admitted to the hospital, are finally being asked to assist in quality improvement projects. Committee meetings, protocol development, and teaching exercises concerning inpatient glucose management are now a component of many endocrinologists’ work week.

So, how strong is the evidence basis for said guidelines? The oft-cited but uncontrolled study by Furnary et al. (14), implemented an insulin infusion protocol in the cardiothoracic ICU that is conservative by the standards now being recommended, with a glucose target of 150–200 mg/dl. Over the years of the study, the glycemic target was gradually reduced, making the results more difficult to interpret. In addition, infectious outcomes in treated patients were compared with those of a historical control group in a study that spanned nearly 15 years. Clearly, many additional factors may have contributed to the benefit ascribed to insulin infusion, including improved surgical and anesthetic expertise, the availability of more powerful antibiotics, and other hospital-related quality improvements. In a recent update from this group (15), a reduced mortality was re-
ported with the greatest reduction in those patients whose glucose targets had been lowered to <150 mg/dl—well above the cut points recommended by the ACE.

The famous Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study applied glucose and insulin infusion in diabetic patients following an acute myocardial infarction (12). The protocol's blood glucose target was also somewhat conservative by the standards recently proposed. Of greater methodological concern, all subjects randomized to insulin infusion additionally received an aggressive multidose insulin injection regimen postdischarge. Therefore, it is impossible to conclude whether the inpatient or outpatient aspects of the DIGAMI protocol (or both) drove the risk reduction. Most notably, the glycemic control achieved in the intensive insulin group consisted of a mean glucose reduction to 173 mg/dl at 24 h and to 144 mg/dl at hospital discharge, again well above the ACE cut points. Furthermore, the mortality reductions were restricted to postinfarct diabetic patients and cannot be necessarily extrapolated to all critically ill hyperglycemic patients.

The preliminary results of the DIGAMI-2 study failed to confirm any benefits on mortality from an intravenous insulin regimen in a similar group of patients (17). In this trial, ~1,300 patients with type 2 diabetes following acute myocardial infarction were randomized to three groups and followed for a mean of nearly 2 years. The first received intravenous insulin and a strict outpatient insulin regimen upon discharge, the second received intravenous insulin only, and the third was assigned to conventional diabetes care in both inpatient and outpatient settings. At 24 h, baseline fasting blood glucose of 229 mg/dl improved to only 164 mg/dl in both intravenous insulin groups and to 180 mg/dl in the standard group. The negative outcome of the DIGAMI-2 does not necessarily invalidate the initial DIGAMI findings. However, it does reinforce the critical issue of proper inpatient insulin strategies, since one of the study's fundamental limitations was the failure to achieve major differences in glucose control between the treatment groups. This experience underscores one of our major criticisms of the ACE recommendations. Indeed, before heralding possibly unrealistic targets, feasibility studies are first required to confirm that they can be safely and reproducibly achieved and translated to the clinical arena.

The study with the soundest methodology was conducted in a surgical ICU by Van den Berghe et al. (13). This group randomized predominately postoperative patients receiving mechanical ventilation to an aggressive insulin infusion protocol if blood glucose exceeded 110 mg/dl to maintain it between 80 and 110 mg/dl. This group was compared with conventional care, in which intravenous insulin was reserved for those with blood glucose >215 mg/dl, and then only to achieve a target of 180–200 mg/dl. Importantly, only 13% of the patients were known to have diabetes before admission. The study's results were impressive, with the intensive group experiencing a 42% reduced ICU mortality that was mainly the result of less infectious complications. All the benefit was enjoyed by patients in the ICU in excess of 5 days, whereas there was no difference in mortality in patients who were discharged from the ICU sooner. Of note, upon discharge from the ICU to the wards, all patients received standard care, with a target glucose of 180–200 mg/dl, but those previously treated intensively still had a median-adjusted 32% reduction (95% CI 2–55%) in all-cause mortality.

The results of these investigations are notable and, taken together, suggest that glucose levels in critically ill patients should be improved. However, from these, it is difficult to define a precise target. The goal of Van den Berghe et al. was very aggressive at 80–110 mg/dl and forms the basis of the ACE recommendations. This is potentially achievable in most ICUs using the human and technical resources available. But, it is unknown whether similar control and benefits can occur in nonsurgical ICU patients or whether a higher glycemic target, perhaps <130–140 mg/dl, may confer similar benefits with easier and safer implementation. For instance in the medical ICU, where patients are typically older, the potential benefits (but also the risks) of rigid glucose control may be greater (18). The only available data in this setting come from a recent nonrandomized report on intensive insulin management in a heterogeneous medical-surgical ICU population using a very structured and "nurse-friendly" protocol on 800 consecutive patients over a 1-year period, as compared with a historical control of similar number of patients the year before (19). The glycemic target was to maintain glucose levels <140 mg/dl using subcutaneous insulin, guided by close blood glucose monitoring.

Continuous intravenous insulin was implemented if the glucose exceeded 200 mg/dl on two consecutive occasions. The mean blood glucose achieved in the insulin protocol group was 131 mg/dl and was associated with hospital mortality reduction of 29%. This result is quite impressive and basically similar to the overall in-hospital mortality reduction of 34% in the highly intensive Leuven protocol that achieved a much lower mean blood glucose of 103 mg/dl. Still, properly controlled randomized studies are warranted to confirm these important findings in different institutions and across the variety of critical care settings. Whereas the proposed ICU cut points are at least based on the results of one well-designed randomized study, the proposed glucose targets for noncritically ill patients are based on essentially no clinical trial data whatsoever. We would agree that most hospitalized patients will likely benefit from the avoidance of severe hyperglycemia and, perhaps, from even tighter glucose control. However, the targets chosen by the ACE are essentially arbitrary and not necessarily consistent with the more severe degree of hyperglycemia that has actually been associated with increased morbidity. In the very thorough ADA technical review (16), several studies are cited as proof of a beneficial effect of glucose control in the noncritically ill (20–22). However, the vast majority are meta-analyses or observational datasets, with many using admission blood glucose concentrations as the sole measure of glucose control. Based on such cross-sectional data alone, it is impossible to extrapolate the effect of inpatient glucose management protocols on clinical outcomes. Obviously, the admission glucose value may well be just an epiphenomenon or merely a reflection of sicker patients. Conclusions drawn from admission glucose values are meaningless in the absence of prospective intervention data.

Are there potentially detrimental effects from such rigid standards? Indeed there are, given the limitations with the current staffing and standards of nursing care in most hospitals. Hypoglycemia is a
frequent adverse effect of strict glucose control (23). In the commonly encountered hospitalized patient with altered cognitive status, due to the effects of age, illness, or psychotropic medications, the typical symptoms of impending hypoglycemia are not properly perceived. In the cardiac patient, hypoglycemia may result in excess catecholamine release that may aggravate myocardial ischemia or have proarrhythmic or cardiovascular consequences (24,25). In poststroke patients, inadequate brain blood glucose supply may worsen cerebral function (26). The risk-benefit ratio of strict glycemic control in all hospitalized patients must take into account the negative implications of more frequent hypoglycemic events.

Before any stringent guidelines are implemented, a major restructuring of hospital care and professional diabetes education will need to occur. We would therefore implore the diabetes community to conduct and funding agencies to support well-designed clinical trials to better assess the benefits and risks of tight glucose control in the inpatient setting. Until such data are available, we would propose the following simple, admittedly more conservative guidelines.

1) On the general medical and surgical wards, persistent hyperglycemia (>200 mg/dl) should be avoided (27), as guided by the patient’s individual clinical situation. The current ADA ambulatory guideline for preprandial plasma glucose levels is 90–130 mg/dl. So, in the absence of specific data, an advisable in-hospital target is to maintain preprandial glucose levels between 90 and 150 mg/dl. This is admittedly somewhat arbitrary but will provide clinicians with a “glycemic cushion” as they strive for reasonable and safe inpatient diabetes care.

2) Because the effects of postprandial hyperglycemia in acutely ill patients are unknown, and because overly frequent insulin dosing may lead to hypoglycemia, in general there is little advantage in assessing postprandial glucose in hospitalized patients, especially when the timing of meals is unpredictable.

3) In general, regular insulin by sliding scale as the sole form of glucose control should be abandoned (28). Basal/bolus insulin coverage should be used instead to provide more physiologic insulin replacement. Clearly, this may not be practical in every patient for a variety of reasons, most especially those in the hospital for short durations. In those circumstances, individualized approaches will be necessary, such as adding supplemental prandial insulin to preexisting simpler insulin regimens. The quality of glucose control should be paramount, not necessarily the method by which this is achieved.

4) In selected patients well controlled on oral agents in whom there are no contraindications and who are expected to eat regularly during the hospitalization, continuation of the ambulatory regimen with or without supplemental preprandial or basal insulin is appropriate. Caution is obviously necessary in the setting of metformin therapy, since hospitalized patients frequently have or are at risk for at least a temporary contraindication to its use.

5) In the ICU, we propose the use of a “trigger” glucose level of 140 mg/dl to prompt initiation of insulin replacement therapy, with the goal of achieving glucose levels as close to normal as possible with avoidance of any symptomatic hypoglycemia or any blood glucose <70 mg/dl. If specific and successful protocols for subcutaneous insulin protocols are available, they can be attempted initially, but intravenous insulin infusions are more reliably successful and preferable, especially as the initial blood glucose concentration climbs higher (29).

6) In markedly hyperglycemic patients, the use of insulin infusions should also be encouraged in non–critical care settings, but hospitals must first provide the care support necessary for the safe implementation of specific protocols.

7) Each hospital should identify multidisciplinary teams, including endocrinologists, nurses, nutritionists, pharmacists, and quality improvement experts to promote strategies for improving glucose control (30,31).

Multiple questions remain. What is the most effective and safest way to improve glucose control in different settings? Given the major knowledge deficits about insulin therapy in the acute care setting of both our primary care colleagues and our trainees, what educational efforts are required? These physicians are justifiably preoccupied with the primary reason for the admission—sometimes life-threatening infectious or cardiovascular complications of diabetes. Understandably, glucose control takes a back seat to these seemingly more pressing concerns. It is therefore quite likely that even with new guidelines, various “contextual factors” will prevent adherence (32). In this light, the many barriers to achieving tight glycemic control in the inpatient setting (6,33) must be overcome. To best assist our primary care and subspecialist colleagues, specific inpatient protocols will need to be carefully developed and validated for both safety and efficacy (34).

Our final caution is regarding the medicolegal implications of the recent recommendations (35,36). Is the individual with an occasional postprandial blood glucose reading of 185 mg/dl and a nonhealing foot ulcer receiving substandard care? Is the diabetologist, part of the team managing the critically ill patient, liable because the average blood glucose was 146 mg/dl and the patient succumbed to his or her illness? Is the elderly patient recovering from pneumonia with fasting glucose of 127 mg/dl receiving suboptimal care? Should insulin therapy have been initiated in each of these patients during their hospitalizations?

Clinical recommendations, especially those concerning a condition as common as inpatient hyperglycemia, must be as evidence-based as possible. Our concern is not in the intention of the ACE guidelines but in the scientific analytical rigor with which they have been formulated and promoted. The call to arms for rigid inpatient glucose control may indeed be premature.

SILVIO E. INZUCCHI, MD1
JULIO ROSENSTOCK, MD2

From the 1Section of Endocrinology, Yale University School of Medicine, New Haven, Connecticut; and the 2Dallas Diabetes and Endocrine Center, Dallas, Texas.

Address correspondence to Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center, 7777 Forest Ln. C-618, Dallas, TX 75230. E-mail: juliorosenstock@dallasdiabetes.com. © 2005 by the American Diabetes Association.

References


