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COMMENTARY

Intensive Control of Diabetes in the Hospital: Why, How, and What Is in the Future?

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Abstract

Intensive management of diabetes is identified as a critical component of inpatient care. However, the fundamental question that remains is whether controlling glycemia in noncritically ill diabetes patients at the lower end of the current guidelines improves outcomes of hospitalization, long-term outcomes of the primary condition, and long-term outcomes of diabetes compared with average glycemia greater than 180 mg/dl. A group of clinical investigators—Planning Research in Inpatient Diabetes (PRIDE)—is preparing randomized controlled trials with the hope of defining optimal glycemic targets for hospitalized patients with diabetes. Given the variety of clinical situations that can occur in the inpatient setting, many medical centers have established dedicated inpatient diabetes teams. There is ample evidence, albeit retrospective, that these teams improve inpatient glucose control and reduce lengths of hospital stays. Using hospitalization as an opportunity to educate patients about diabetes and to optimize their treatment regimen may improve long-term outpatient glycemic control.

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Introduction

The Diabetes Control and Complication Trial[1] and the United Kingdom Prospective Diabetes Study[2] have established new standards for diabetes therapy. They have convincingly demonstrated that better control prevents and delays chronic complications of diabetes. As a result, outpatient diabetes management is more aggressive and intensive than in the past. Similarly, the landmark intensive care unit (ICU) study by Van den Berghe and colleagues[3] has significantly altered our approach toward treatment of diabetes and hyperglycemia in hospitalized patients. Their report inaugurated a movement toward intensive glucose control in the inpatient setting, with the goal of achieving normoglycemia.

In both cases, however, the studies that followed these original publications have begun challenging some of the earlier postulates. Outpatient studies suggested that aggressive therapy with goals of achieving glycohemoglobin under 6% may have detrimental consequences in some patients and did not substantially improve outcomes in others.[4–6] At the same time, controversies have been brought into intensive inpatient diabetes

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Abbreviations: (ACP) American College of Physicians, (DM) diabetes mellitus, (ICU) intensive care unit, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation, (NPO) *nil per os*, (PRIDE) Planning Research in Inpatient Diabetes, (TPN) total parenteral nutrition

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management. Not only have some studies failed to demonstrate significant advantages of tight glycemic control,[7] but other studies have reported a potentially detrimental effect of tight control in hospitalized patients.[8,9] Thus, both the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) and Glucontrol studies were terminated early due to an increased risk of mortality and severe hypoglycemia in the intensive treatment arms.

As the proverbial pendulum swings, the question of the importance of glycemic control in hospitalized patients awaits definitive answers from randomized controlled trials.

A Case for Glycemic Control in the Hospital

Diabetes mellitus (DM) is highly prevalent in the United States; approximately 25 million cases were reported in 2010.[10] Fifty percent of direct medical expenditures for diabetes, $58 billion per year, are attributed to hospitalization costs.[11] These costs are certainly an underestimation, as a significant number of patients with no known history of diabetes have random glucose >200 mg/dl during their hospitalization[12] or hemoglobin A1c >6.1%.[13]

Intensive management of diabetes, recognition of newly diagnosed diabetes, and management of hyperglycemia are increasingly identified as critical components of inpatient care. Diabetes is associated with increased hospital admissions, length of hospital stays, and an annual per capita cost ratio of 2.3:1 compared to nondiabetic patients.[11] There is much evidence that hyperglycemia itself, regardless of known diabetes, is associated with increased inpatient morbidity and mortality. Studies have shown such associations in the settings of stroke, acute myocardial infarction, general and vascular surgery, renal transplantation, community-acquired pneumonia, and total parenteral nutrition (TPN) recipients.[14–21] Hyperglycemia is also an independent marker of in-hospital mortality, and patients with undiagnosed diabetes have an 18-fold greater risk for death than patients without diabetes.[22] Studies in general and cardiothoracic surgery have shown significant improvement in outcomes with correction of hyperglycemia.[23,24]

Mechanistically, hyperglycemia has been shown to impair polymorphonuclear neutrophil cell function and enhance oxidative stress and production of cytokines, leading to inadequate antimicrobial defense with poor bacterial clearance.[25–28] At the same time, hyperglycemia induces endothelial dysfunction, a procoagulant state, and disrupts water-electrolyte balance,[29–31] thus resulting in greater morbidity in hospitalized patients with diabetes.

Whereas there is little doubt that severe hyperglycemia must be avoided, an optimal target glucose range for hospitalized patients with diabetes remains undefined, and is continuously debated.

What is the Optimal Range of Glycemia in Hospitalized Patients?

Even though the initial Van den Berghe study[3] had suggested that attainment of normoglycemia in the ICU patients might be best for outcomes, subsequent studies failed to fully support this notion, and revealed unacceptably high rates of hypoglycemia as a price patients paid for this effort.[7–9]

While many studies have shown a clear association between hyperglycemia and morbidity and mortality, none has demonstrated a threshold glucose level at which the risks of hyperglycemia suddenly increase. One study observed that ICU patients with the highest survival rate had glucose levels 111–144 mg/dl, whereas the highest rate of mortality was in the cohorts with glucose levels >200 mg/dl.[32]

Current guidelines for inpatient glycemic control recommend that blood glucose levels be maintained in the 140–180 mg/dl range as long as these targets can be achieved safely.[33] This compromise appears to be accepted by the American Diabetes Association, American Association of Clinical Endocrinologists, and by the American College of Physicians (ACP).

Published ACP clinical practice guidelines are based on a meta-analysis of inpatient diabetes studies.[34] These guidelines recommend that intensive insulin therapy not be used for either ICU or general ward patients, and recommends a target glucose range of 140–200 mg/dl. However, caution must be used when interpreting results from a meta-analysis, as the primary outcomes, patient populations, and target blood glucose ranges differed among the studies. Falciglia and colleagues[35] observed that mortality rates among patients with diabetes in 117 surgical, medical, and cardiac ICUs, as well as the effect of hyperglycemia, varied significantly depending on the admission diagnosis, strongly suggesting that one should not combine all patients with diabetes together when examining the influence of glycemic control on morbidity and mortality.

Determining the ideal lower boundary of target blood glucoses in hospitalized patients is more straightforward than the upper boundary, as the definition of hypoglycemia is generally accepted as <70 mg/dl, and severe hypoglycemia <40 mg/dl. Independent predictors of severe hypoglycemia include duration of insulin treatment, glomerular filtration rate less than 60 ml/min, presence of peripheral neuropathy (presumably as a marker for increased risk of autonomic neuropathy), and past history of severe hypoglycemia.[36] The aforementioned inpatient studies demonstrated significantly increased rates of hypoglycemic events in the intensive arms, though only NICE-SUGAR has observed increased mortality associated with hypoglycemia. Although the increased mortality was predominantly from cardiovascular events, it is uncertain whether hypoglycemia itself is the direct cause of mortality or whether it is a surrogate marker for poor health.[37]

While it is clear that some glucose control is beneficial, the fundamental question is whether or not controlling glycemia in noncritically ill patients with diabetes at the lower end of the current guidelines improves outcomes of hospitalization as compared with average glycemia >180 mg/dl. The Planning Research in Inpatient Diabetes (PRIDE) group is preparing randomized controlled trials with the hope of defining the optimal glycemic targets for hospitalized patients with diabetes.

How Do We Achieve Desired Glucose Control?

Insulin is the cornerstone of inpatient glucose management. Aside from a lack of published studies examining outcomes of hospitalized patients on oral agents, there are several reasons for favoring insulin use in the inpatient setting. Hospitalized patients with diabetes are often unable to take oral medications, whether because of illness or being kept *nil per os* (NPO) or because they frequently have contraindications to the use of oral medications (e.g., contrast studies for metformin and congestive heart failure for thiazolidinediones).

Recommendations for insulin dosing are based on three components: basal, prandial (nutritional), and correction (to account for hyperglycemia above the desired targets). The goal is to adjust basal and prandial insulin regimens so that correction doses of insulin are minimized. Scheduled insulin doses are more efficacious in controlling glucose levels than sliding scale.[38–41] Sliding-scale insulin administration fails to control glucose levels because it is a reactive treatment for hyperglycemia that has already occurred. More importantly, it neglects to treat a patient's basal insulin requirements—an absolute necessity in insulinopenic patients such as those with type 1 DM.

With rapid advances in technology of continuous glucose monitoring as well as in closed-loop insulin delivery there is significant optimism that glycemic control in hospitalized patients will improve dramatically.[42]

Transitions of Care

Of unique importance in the care of hospitalized patients with diabetes is recognizing and becoming adept at treating hyperglycemia through multiple transitions of care. Transitions of care begin when the patient is admitted to the hospital and end upon hospital discharge. Between these two points, there are several transitions within the hospital admission that affect glycemic control. There are acute changes in oral intake resulting from various gastrointestinal symptoms, inability to eat or swallow, and NPO orders in preparation for a procedure, to name a few. There are changes in physical activity, from bed rest in an ICU to daily exercise in the rehabilitation unit. Medications, such as steroids, increase insulin resistance and organ dysfunction, such as acute renal failure, alters insulin clearance rates. Enteral and parenteral nutrition as well as infusions of dextrose-based solutions profoundly influence glycemic excursion and insulin requirements. In many hospitalized patients, maintaining glycemia in the target range is far from being a trivial task. The ideal insulin regimen for a hospitalized patient is subject to change more frequently and at any given time, compared to the relatively healthy, stable patient at home.

Most medical centers have developed specific protocols to aid in the initiation and transition of diabetes care in the hospital. However, many clinical dilemmas remain. For example, patients receiving TPN or enteral tube feeding warrant their own treatment protocols, as it has been observed that 77% of patients with type 2 DM required an extra 100 units/day of insulin while receiving supplemental nutrition.[43] In many institutions, insulin is added to the TPN bag, while other hospitals treat patients with diabetes on TPN with various regimens of subcutaneous insulin. Similarly, there is no consensus on how to combat steroid-induced hyperglycemia. We have demonstrated that neutral protamine Hagedorn insulin administered concurrently with intravenous methylprednisolone is efficacious in controlling steroid-induced hyperglycemia.[44] The PRIDE group is addressing some of these questions, and is attempting to design multi-center

clinical trials to identify the most efficacious ways of controlling hyperglycemia in various clinical situations.

One of the most pressing problems in the care of patients with diabetes is their transition from inpatient to outpatient settings.[45] While in the hospital, depending upon their clinical situation, patients may have been treated with higher or lower doses of insulin than they required prior to hospitalization. With short lengths of stay in the hospital, many patients with diabetes are discharged on doses of insulin dramatically different from and not necessarily safe for their outpatient lifestyle. Inadequate or untimely adjustment of the discharge insulin dose may jeopardize patient safety, leading to hypoglycemia or hyperglycemia shortly after discharge.[45] Both hypo- and hyperglycemia may necessitate ambulance calls, emergency department visits, and readmissions, thus significantly increasing health care costs.

Given the variety of clinical situations that can occur in the inpatient setting, it is common for medical centers to establish an inpatient diabetes team dedicated to managing inpatient hyperglycemia through these transitions. There is ample evidence that these teams improve inpatient glucose ranges, and with early consultation, they may reduce hospital lengths of stay.[46–49] Perhaps most significantly, using hospitalization as an opportunity to educate a patient about diabetes and to optimize their treatment may improve long-term outpatient glycemic control.[49,50]

Conclusion

As the prevalence of diabetes rises, so does the prevalence of hyperglycemia in hospitalized patients, and the incidence of hospital admissions for patients with diabetes. Evidence suggests that glucose control and avoidance of hypoglycemia are beneficial for positive outcomes in the hospitalized patient. It is less clear, however, whether more liberal control might have detrimental influence on the outcomes of a given hospitalization, on long-term outcomes of the primary condition, or on long-term outcomes of diabetes. Randomized clinical trials are clearly needed to define any clinical significance of targeted glucose control and threshold for impact of glycemia on health care outcomes. Such studies must be conducted in diverse clinical settings such as general medicine and surgery patients, and in specific circumstances such as acute stroke, cystic fibrosis-related DM, and cardiovascular disease. It is also important to confirm the impact of specialist care by diabetes management teams and inpatient education on short- and long-term outcomes. The goal of the PRIDE group is to establish a body of evidence to define standards of care in this relatively new, yet increasingly important, field of diabetology.

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