# Hospital Hypoglycemia: From Observation to Action

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## ABSTRACT

**Background:** A preponderance of evidence indicates that when treatment of hyperglycemia with insulin is provided for certain hospitalized populations, the attainment of appropriate glycemic targets improves nonglycemic outcomes such as mortality rates, morbidities (eg, wound infection, critical illness polyneuropathy, bacteremia, new renal insufficiency), duration of ventilator dependency, transfusion requirements, and length of hospital stay. Nevertheless, randomized controlled trials (RCTs) of intensive insulin therapy and studies of outcomes before and after implementation of tight glycemic control have consistently recognized an increased incidence of hypoglycemia as a complication associated with the use of lower glycemic targets and higher doses of insulin.

**Objectives:** This commentary compares the quality of the available evidence on the clinical impact of iatrogenic hypoglycemia. We present treatment strategies designed to prevent iatrogenic hypoglycemia in the hospital setting.

**Methods:** The PubMed database and online citations of articles tracked subsequent to publication were searched for articles on the epidemiology, clinical impact, and mechanism of harm of hypoglycemia published since 1986. In addition, we searched the literature for RCTs conducted since 2001 concerning intensive insulin therapy in the hospital critical care setting, including meta-analyses; letters to the editor were excluded. The retrieved studies were scanned and chosen selectively for full-text review based on the study size and design, novelty of findings, and evidence related to the possible clinical impact of hypoglycemia. Reference lists from the retrieved studies were searched for additional studies. Reports were summarized for the purpose of comparing and contrasting the qualitative nature of information about iatrogenic hypoglycemia in the hospital.

**Results:** Eight RCTs of intensive glycemic management, 16 observational studies of hospitalized patients with hypoglycemia (including studies of outcomes before and after implementation of tight glycemic control), and 4 case reports on patients with hypoglycemia were selected for discussion of the incidence of hypoglycemia, significance of hypoglycemia as a marker or cause of poor prognosis, and clinical harm of hypoglycemia. Hypoglycemia was identified in clinical trials as either a category of adverse events or a complication of intensified insulin treatment. For example, a recent meta-analysis found that the incidence of severe hypoglycemia was higher among critically ill patients treated with intensive insulin therapy than among control patients, with a pooled relative risk of 6.0 (95% CI, 4.5–8.0). In the largest multisite RCT on glycemic control among patients in intensive care units (ICUs) conducted to date, deaths were reported for 27.5% (829/3010 patients) in the intensive-treatment group and 24.9% (751/3012 patients) in the conventional-treatment group (odds ratio, 1.14; 95% CI, 1.02–1.28; $P = 0.02$). In another multisite ICU study, although the intensive and control groups had similar mortality rates, the mortality rate was higher among hypoglycemic participants than among nonhypoglycemic participants (32.2% vs 13.6%, respectively; $P < 0.01$). Pooled data from 2 single-site studies in medical and surgical ICUs revealed an increased risk of hypoglycemia in the intensive-treatment group compared with the conventional-treatment group (11.3% [154/1360] and 1.8% [25/1388], respectively; $P < 0.001$), but the hospital mortality rate was similar for the 2 groups (50.6% [78/154] and 52.0% [13/25], respectively). Specific sequelae of hypoglycemia affecting individual patients were described in the RCTs as well as in the observational studies. New guidelines for glycemic control have recently been issued, but results of the studies using the new targets are not yet available. We propose treatment strategies designed to prevent iatrogenic hypoglycemia in the hospital setting.

**Conclusions:** In response to the growing evidence on the risk of hypoglycemia during intensified glycemic management of hospitalized patients, professional organizations recently revised targets for glycemic control. It is appropriate for institutions to reevaluate hospital protocols for glycemic management with intravenous insulin and, on general wards, to implement standardized order sets for use of subcutaneous insulin to achieve beneficial targets using safe strategies. (*Insulin*. 2010;5:16–36) © 2010 Excerpta Medica Inc.

**Key words:** hypoglycemia, hypoglycemic agents, hospitalization, critical care, hyperglycemia.

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## INTRODUCTION

Observational studies support the belief that development of hyperglycemia in the hospital is associated with poor outcomes across a wide variety of settings.[1–9] The possibility that outcomes could be modified by control of hyperglycemia has been addressed in pre- and postinterventional studies[10–13] as well as in randomized controlled trials (RCTs).[14–26] Several of these RCTs have addressed the question of whether strict glycemic management is capable of modifying outcomes favorably in the general surgical, medical, or mixed intensive care unit (ICU) setting.[15,18–20,22–26]

Trials of intensive glycemic management designed to achieve lower glycemic targets have shown inconsistent benefits regarding study end points, a higher insulin requirement, and a higher incidence of hypoglycemia. Therefore, the question of whether iatrogenic hypoglycemia is tolerable underlies the current controversy on intensive glycemic management of hospitalized patients. A related question is whether end points of the RCTs were affected by glycemic variability and/or development of hypoglycemia. Under the broad strokes of a program of strict control believed to ensure the greatest good for the greatest number of patients, individual patients might suffer consequences of hypoglycemia that are fatal or life changing. In response, professional organizations that previously had introduced stringent targets for glycemic control now have recommended glycemic targets thought to be attainable with less risk of hypoglycemia.[27–31]

If iatrogenic hypoglycemia is tolerable at some level, the limits of that tolerability must be determined. The answer would require consideration of setting; patient characteristics and comorbidities; incidence, duration, and severity of iatrogenic hypoglycemia; and the counteracting individual and population advantages that might accrue from glycemic control according to patient condition such as mortality rates, morbidities (eg, wound infection, critical illness polyneuropathy, bacteremia, new renal insufficiency), duration of ventilator dependency, transfusion requirements, and length of hospital stay.

Hypoglycemia has been studied under experimental conditions in humans. However, there never will be an RCT in the acute care setting in which some participants are assigned to a strategy that will produce hypoglycemia to compare outcomes of patients with hypoglycemia versus those without hypoglycemia. Information about hypoglycemia will be collected from RCTs and from studies before and after implementation of improved glycemic control, exploring outcomes other than hypoglycemia, or from observational studies and case reports. When hypoglycemia is studied in the context of RCTs aimed at glycemic control, it may be possible to judge by utilitarian criteria whether the benefits of strict glycemic control offset any negative consequences of hypoglycemia resulting from the intervention. Analysis may be confounded by underreporting of events, inability to isolate direct consequences of hypoglycemia from consequences of comorbidities, and incomplete knowledge of consequences partially attributable to hypoglycemia that could be multifactorial, indirect, delayed, or cumulative. RCTs and prospectively implemented intensive-control programs are likely to use protocols for prevention of hypoglycemia and for prompt correction of any episodes of hypoglycemia that might occur.

Safeguards required in the context of research are not necessarily ensured during ordinary practice. Reliance on the incidences of adverse events attributable to hypoglycemia in the research context may lead to underestimates of the risk of hypoglycemia using the same glycemic targets in ordinary clinical settings. Furthermore, the timing of sampling under some research protocols may fail to detect actual episodes of hypoglycemia, and statistical reports summarizing the results of clinical trials generally fail to provide the richness of detail found in case reports. The best information on the consequences of hypoglycemia obtained from clinical trials may require subgroup analysis. For all these reasons, not only must we make the best possible use of the adverse event data from clinical trials and from studies of outcomes before and after implementation of improved glycemic control,[13,32] but we also should consider that other observational studies dedicated to the question of hypoglycemia and case reports may provide a better understanding of the real-world risks of hypoglycemia.

In this commentary, we briefly discuss the importance of epidemiologic data on hypoglycemia.[8,32–51] We separately consider the incidence of hypoglycemia, the possibility that hypoglycemia is a marker of severity of disease, and the possibility that hypoglycemia directly causes harm. We emphasize the descriptive and deontologic importance of anecdotal reports to our understanding of hospital hypoglycemia and the value of case reports, including case descriptions embedded within larger statistical studies.[21,52–56] We also propose management strategies for both intravenous and subcutaneous insulin therapy.

## METHODS

We searched the PubMed database and online citations of articles tracked subsequent to publication for articles on the epidemiology, clinical impact, and mechanism of harm of hypoglycemia published since 1986, the year in which a seminal article by Fischer et al[34] was published. In addition, the literature was searched for RCTs or meta-analyses on intensive insulin therapy in the hospital critical care setting since 2001, when the first study of strict glycemic control was conducted in a Leuven, Belgium surgical ICU.[15] Reference lists from the retrieved articles were searched for additional studies. Letters to the editor were excluded. Reports were summarized for the purpose of comparing and contrasting the qualitative nature of information about iatrogenic hypoglycemia in the hospital.

## RESULTS

From the literature search, articles were chosen selectively for full-text review based on study size and design, novelty