Does glycemic control with insulin therapy play a role for critically ill patients in hospital?

Hyperglycemia commonly occurs in critically ill patients. Indeed, a link between critical illness and hyperglycemia was recognized as early as the late 19th century, with the coining of the term "stress hyperglycemia." In-hospital stress hyperglycemia, especially of new onset, has often been seen as an adaptive response to heightened medical stress and considered a marker of illness severity rather than a distinct medical condition requiring management.

Recent evidence, however, challenges that notion. Several observational studies published over the last decade have established that in-hospital hyperglycemia is an independent risk factor for adverse outcomes, including death, particularly in critically ill patients with known diabetes but also in patients with new-onset hyperglycemia. Additional evidence from recently completed randomized trials (Table 1) have led the American Diabetes Association and the American Association of Clinical Endocrinologists to issue guidelines recommending a fasting glucose target of less than 6.1 mmol/L in hospital patients regardless of their history of diabetes or severity of illness.

Experimentally, the concept of altering glycemia in hospital patients to affect outcomes was first introduced in the 1960s, when an infusion of glucose, insulin and potassium (GIK) was developed as a potential therapy to improve cardiac-related outcomes following acute myocardial infarction (Box 1). Multiple small studies of GIK completed over the next 30 years reported conflicting results, which could have been due, at least in part, to the differences in the various regimens used. The first large study of a glucose–insulin infusion aiming at euglycemia was the DIGAMI study (Table 1), in which patients with diabetes and acute myocardial infarction were randomly assigned to receive either routine therapy or intensive therapy with a glucose–insulin infusion for 48 hours to attain a glucose target of less than 10 mmol/L, followed by subcutaneous insulin therapy. Although the intensive therapy did not result in a statistically significant benefit in the short term, it was associated with a reduction of 26% in the relative risk of death at 1 year compared with routine therapy.

The DIGAMI study was the first to provide concrete evidence that gly-

DOI:10.1503/cmaj.051418

Table 1: Major randomized controlled trials of insulin therapy in critically ill patients

Study	Study population	Insulin-based intervention	Glucose goal, mmol/L	Outcomes
Malmberg et al (DIGAMI)*	Patients with diabetes and acute MI	Intensive acute and long-term therapy (n = 306) Routine therapy (n = 314)	7-10 None	No difference between groups in short-term (in-hospital) mortality; reduction in long-term (outpatient) mortality (26%) with intensive therapy
Van den Berghe et al†	Adult surgical ICU patients (63% cardiac surgery)	Intensive IV therapy (n = 765) Routine therapy (n = 783)	4.4-6.1 10.0-11.1	Reductions with intensive therapy in in-hospital mortality (34%) and rates of blood-borne infections (46%), acute renal failure (41%), transfusions (50%) and critical illness polyneuropathy (44%)
Mehta et al (CREATE-ECLA)‡	Patients with acute MI	24-h glucose-insulin-potassium (GIK) IV infusion (n = 10 110) Routine therapy (n = 10 091)	None None	No difference between groups in 30-day mortality or rates of cardiac arrest, cardiogenic shock, reinfarction or heart failure
Malmberg et al (DIGAMI 2)§	Patients with type 2 diabetes and acute MI	Intensive acute and long-term therapy (n = 474) Intensive acute therapy and routine long-term therapy (n = 473) Routine acute and long-term therapy (n = 306)	7-10 (acute) 5-10 (long-term) 7-10 (acute) None (long-term) None	No difference between groups in short-term (in-hospital) or long-term (outpatient) mortality

Note: MI = myocardial infarction, ICU = intensive care unit, IV = intravenous.
*Malmberg et al. *J Am Coll Cardiol* 1995;26(1):57-65.
†Van den Berghe et al. *N Engl J Med* 2001;345(19):1359-67.
‡Mehta et al. *JAMA* 2005;293(4):437-46.
§Malmberg et al. *Eur Heart J* 2005;26(7):650-61.

Box 1: Potential mechanisms to explain benefits of insulin therapy and glycemic control in critically ill hospital patients

- Improved immune function and decreased susceptibility to infection
- Decreased systemic and cellular inflammation
- Improved endothelial function (through improvement in vasomotor function and stimulation of nitric oxide production)
- Improved coagulable state owing to enhanced fibrinolysis and platelet function
- Decreased triglyceride and increased high-density lipoprotein cholesterol levels
- Increased size of low-density lipoprotein cholesterol
- Anabolic effects of insulin
- Improved myocardial function
- Decreased circulation of free fatty acids
- Suppression of free fatty acid uptake
- Increased glucose uptake
- Improved contractility
- Direct effect of potassium in glucose-insulin-potassium solutions on myocardial function

cemic control in hospitalized patients may improve outcomes. However, it was not until 2001, when the results of a study by Van den Berghe and colleagues were published (Table 1), that hyperglycemia in critically ill patients and its therapy with insulin became of great interest to clinicians. In this randomized controlled trial, patients admitted to the surgical intensive care unit (ICU), 63% of whom had undergone cardiac surgery, were treated with either routine therapy or intensive insulin therapy aiming at tight glycemic control. The results were remarkable: the intensive insulin therapy resulted in a glucose level of 5.7 mmol/L, as compared with 8.5 mmol/L in the control group, and significantly reduced in-hospital mortality and morbidity.

Since then, 2 studies of insulin therapy in hospital patients were published, with neutral results. The CREATE-ECLA study was an international trial involving patients with acute myocardial infarction who were randomly assigned to receive upon hospital admission either GIK infusion for 24 hours (without a glucose target) or usual care (Table 1). No difference between the 2 groups was seen in mortality or morbidity. The results of this trial suggest that insulin therapy without targeting euglycemia probably has no effect on outcomes.

The DIGAMI 2 study tried to distinguish the short-term from the long-term benefits of an insulin-based glucose management protocol by randomly assigning hospital patients with acute myocardial infarction into 3 groups (Table 1). No differences in mortality or morbidity were found between the 3 groups. DIGAMI 2 did not support the concept that acute insulin therapy continued over the long term decreased mortality among diabetes patients with acute myocardial infarction any better than conventional therapy. However, this study was underpowered by not meeting enrolment numbers and did not achieve its treatment goals.

We recently conducted a systematic review and meta-analysis of data from 35 randomized trials to determine the effect of insulin therapy begun in hospital on mortality among patients with critical illness (acute myocardial infarction, stroke, cardiac surgery or an illness requiring a stay in the ICU).[1] The combined results showed that insulin therapy decreased short-term mortality by 15%. In subgroup analyses, insulin therapy was found to be effective in the surgical ICU, when the aim of therapy was glucose control, and in patients with diabetes.

Various glucose-dependent and glucose-independent mechanisms have been proposed in an effort to explain the adverse effects of in-hospital hyperglycemia on patient outcomes and the potential benefit of insulin therapy (Box 1). However, hyperglycemia per se may not be an independent risk factor for death, but it may be a marker of insulin resistance and associated conditions such as increased systemic inflammation, endothelial dysfunction, and impaired fibrinolysis and platelet dysfunction, which lead to hypercoagulability, endothelial injury and increased risk of thrombotic events. The relative contribution of the glucose-lowering effects of insulin versus its glucose-independent effects on systemic inflammation, endothelial function and fibrinolysis is yet to be elucidated, but it is likely that both mechanisms operate in conjunction to affect outcomes.

In conclusion, we agree with the recommendations by the American Diabetes Association and the American Association of Clinical Endocrinologists that improved glycemic control should be an important component of care for patients admitted to hospital. However, although the evidence supports tight glucose control in cardiac patients in the surgical ICU, we believe that the recommended degree of strict glycemic control in all hospital patients is premature and not supported by current evidence. Specifically, there are no prospective randomized trials involving patients on medical or surgical wards, and the available observational studies are retrospective and therefore limited. Results from a recently completed trial in the medical ICU are forthcoming. Until further evidence becomes available, it is prudent for clinicians to aim for a fasting glucose level of less than 8 mmol/L in all hospital patients, with stricter glucose targets in critically ill patients, especially those with cardiac disease.

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Competing interests: None declared for Arpita Patel. Anastassios Pittas will be directing a CME program (Hyperglycemia and Insulin Use in the Hospital Setting) that has been supported in part by funds from Novo Nordisk and Lifescan, manufacturers of insulin products and glucose monitors; these companies have not influenced the content of the CME program in any way.

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