Hyperglycemia in Acutely Ill Patients

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MOST PHYSICIANS WILL ENcounter acutely ill patients who develop hyperglycemia. A third of all persons admitted to an urban general hospital had fasting glucose levels exceeding 126 mg/dL (7 mmol/L), or 2 or more random glucose levels exceeding 200 mg/dL (11.1 mmol/L); a third of those patients with hyperglycemia did not have a prior diagnosis of diabetes.[1] Physicians often perceive hyperglycemia as a consequence of stress that runs parallel to the clinical course of an acute illness. Clinicians often start treatment of hyperglycemia only after glucose levels have exceeded 200 to 250 mg/dL (11-14 mmol/L). One reason for this is the perception that avoidance of hypoglycemia and its potential consequences is more important than glycemic control while patients are hospitalized. We discuss the evidence supporting the hyperglycemic milieu as a risk factor for adverse outcomes in the acutely ill patient with and without known diabetes, and we focus on the efficacy and safety of implementing tighter glycemic control for hospitalized patients.

Pathophysiology of Hyperglycemia

In healthy persons without diabetes, the serum glucose concentration is closely regulated. In the overnight fasted state, euglycemia occurs because the rate of hepatic glucose production equals the rate of glucose uptake. Following a meal, the increase in serum glucose is accompanied by a rapid increase in insulin and a prompt decrease in glucagon. These changes result in a decrease in hepatic glucose production and an increase in peripheral glucose uptake, thereby preventing the peak serum glucose level from exceeding 150 mg/dL (8.3 mmol/L).

During illness, stress increases the concentration of counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hormone) and cytokines. Counterregulatory hormones cause hyperglycemia by increasing hepatic glucose production and by decreasing peripheral glucose uptake. Cytokines, as mediators of the systemic inflammatory response, may have hyperglycemic effects through stimulation of counterregulatory hormone secretion. Similar degrees of stress cause an even greater derangement in glucose metabolism in patients with diabetes who have insulin resistance and impaired insulin secretion. During illness, patients with diabetes may exhibit greater glucose response to counterregulatory hormones and may not sufficiently increase insulin secretion as a compensatory response.

Causes of Hyperglycemia

In patients with and without diabetes, potential causes of hyperglycemia should be sought. Hyperglycemia can result from insufficient doses of insulin (including an inadequate sliding scale administration of short-acting insulin).[2] Unexplained hyperglycemia may be a sign of infection or inflammation due to the effects of increased hormone and cytokine levels. Hyperglycemia can also result from the provision of excessive calories from parenteral and enteral nutrition, as well as from dextrose infusions that are commonly used for fluid resuscitation and for the delivery of medications. For instance, each liter of 5% dextrose or 0.5 L of 10% dextrose provides 170 kcal (from 50 g of dextrose). Medications formulated in fat emulsion such as propofol, a short-acting anesthetic agent used for sedation in the intensive care unit (ICU), provide the same calories (1.1 kcal/mL) as an identical infusion rate of the 10% fat emulsion used in parenteral nutrition. Patients treated with peritoneal dialysis may develop hyperglycemia due to absorption of dextrose from the high-dextrose dialysis fluid. Frequently administered medications that can result in hyperglycemia include corticosteroids, sympathomimetics, and immunosuppressants (eg, cyclosporine, tacrolimus).[3]

Effects of Hyperglycemia

Over the short term, hyperglycemia can adversely affect fluid balance (through glycosuria and dehydration) and immune function, and it can promote inflammation.[4-6] In vitro studies document that hyperglycemia is associated with abnormalities in white blood cell function (granulocyte adhesion, chemotaxis, phagocytosis, respiratory burst and superoxide formation, and intracellular killing). These abnormalities, however, improve with glucose control.[4] In addition, hyperglycemia may also impair complement activity. Glucose, through complement glycation, may compete with microorganisms for the attachment of complement, inhibiting opsonization.

Observational studies indicate that hyperglycemia in patients without diabetes is a risk factor for adverse outcomes during acute illness. Two meta-analyses of observational studies quan-

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tified the impact of hyperglycemia on the prognosis of patients without diabetes following myocardial infarction and stroke.[7,8] In patients who had just experienced myocardial infarction, glucose values in excess of 110 to 144 mg/dL (6.1-8.0 mmol/L) were associated with a 3-fold increase in mortality (odds ratio, 3.9; 95% confidence interval, 2.9-5.4) and a higher risk of heart failure.[7] In patients who had experienced ischemic stroke, glucose values in excess of 6.0 to 8.0 mmol/L (108-144 mg/dL) were associated with a 3-fold increase in mortality (odds ratio 3.1; 95% confidence interval, 2.5-3.8) and appear to be related to the degree of permanent disability after the stroke.[8] Similarly, observational studies in patients with diabetes reveal an increase in the risk of adverse outcomes.[1,7-11]

Randomized trials of interventions in acutely ill patients have also documented an association between hyperglycemia and adverse outcomes. The Veterans Affairs Cooperative Study was designed to test the hypothesis that perioperative parenteral nutrition would prevent serious complications following major surgery.[12] Although patients receiving parenteral nutrition had fewer noninfectious complications, infections were twice as common as in control patients. This higher infection rate was associated with severe hyperglycemia and provision of excess calories. A serum glucose concentration greater than 300 mg/dL (16.6 mmol/L) occurred in 20% of patients receiving parenteral nutrition and in 1% of the control group. Likewise, a meta-analysis of perioperative nutrition conducted 10 years ago showed that the 61% greater infection risk in patients receiving parenteral nutrition compared with enterally fed patients was confounded by the difference in serum glucose levels in the first 5 postoperative days (180 mg/dL [10 mmol/L] vs 150 mg/dL [8.3 mmol/L]).[13] And in a recently published randomized trial of enteral and parenteral nutrition, parenterally fed patients, who had an average maximum serum glucose level of 160 mg/dL (8.8 mmol/L), had 42% more infections than the enterally fed group, who had maximum serum glucose levels of 144 mg/dL (8 mmol/L).[14] Finally, 2 other randomized trials comparing growth hormone with placebo in patients in the ICU after surgery, trauma, or acute respiratory tract failure, showed a 49% to 57% increased risk of mortality in the growth hormone treatment groups. This difference was confounded by 18 to 45 mg/dL (1-2.5 mmol/L) higher glucose values in the growth hormone groups.[15]

Benefits of Controlling Hyperglycemia

Control of hyperglycemia during acute illness, however, has been associated with improved outcomes. In an observational study, the implementation of an insulin infusion to maintain glucose levels between 150 and 200 mg/dL (8.3-11.1 mmol/L) decreased the risk of sternal wound infections following coronary artery bypass graft surgery by 58%.[16] Also, Malmberg[17] conducted a randomized trial of intensive insulin therapy (from admission to 3 months after discharge) in patients with diabetes after myocardial infarction (DIGAMI trial). According to this study, the 1-year mortality rate was 29% lower in patients receiving intensive insulin therapy than in the standard treatment group.[17] In another example, Van den Berghe et al[18] conducted a randomized trial of intensive glycemic control (glycemic goal of 80-120 mg/dL [4.4-6.6 mmol/L]) compared with usual care in a surgical ICU. At the end of the study period, patients with an average blood glucose concentration of 103 mg/dL (5.7 mmol/L) experienced 44% lower mortality than patients with a blood glucose concentration of 153 mg/dL (8.5 mmol/L).[18]

This evidence strongly suggests that hyperglycemia is associated with adverse outcomes for hospitalized patients with and without diabetes (particularly death, disability after acute cardiovascular events, and infections), and that improvement in outcomes can be achieved with improved glycemic control. Postdischarge follow-up may represent an opportunity for primary care physicians to diagnose diabetes and minimize diabetes-related complications. Physicians may also need to determine whether patients with a history of hyperglycemia, while acutely ill, are at high risk of diabetes.[19] The latter patients will require modifications in diet and physical activity, interventions that decrease the incidence of diabetes by 48% to 66%.[20]

Researchers have not elucidated whether the benefits discussed are due to glycemic control or to the correction of relative insulin deficiency. Hyperglycemia, however, could be a modifiable risk factor for adverse outcomes; that is, correction of hyperglycemia (with or without insulin administration) may normalize immune function and limit the extent of neural tissue damage following ischemia. Alternatively, insulin administration (with or without glycemic control) may be responsible for the improved outcomes. Insulin can enhance energy delivery to the ischemic myocardium limiting myocardial damage,[21] and by decreasing circulating fatty acids, insulin may normalize endothelium-dependent vasodilation, replete intracellular calcium, and prevent arrhythmias.[22] And through its anabolic effects, insulin may promote tissue repair and prevent transfusions, dialysis, and critical illness polyneuropathy.[23]

Avoidance of Hypoglycemia

While the technology to deliver tight glycemic control in the critical care setting is widely available (ie, pumps to intravenously infuse short-acting insulin and bedside glucose meters), implementing a safe and effective program may present logistical challenges.[2] One safety concern relates to the potential increase in the risk of hypoglycemia, but interventional studies have reported that patients receiving intensive glycemic control did not have clinically important adverse consequences of hypoglycemia. The DIGAMI trial, for example, reported no difference in the incidence of arrhythmias or ischemic events in patients after myocardial infarction with or without hypoglycemia (defined as glucose level <54 mg/dL [3 mmol/L]).[24] And Van den

Berghe et al reported a 60% increase in the risk of hypoglycemia (defined as glucose concentrations <40 mg/dL [2.2 mmol/L]) but reported no clinically adverse consequences of these episodes.[18] Similarly, a feasibility study of intensive insulin therapy (glucose goal of 72-126 mg/dL [4-7 mmol/L]) in patients after stroke resulted in no episodes of hypoglycemia (no glucose levels <40 mg/dL [2.2 mmol/L]).[25]

The aforementioned trials redesigned the system of delivery of health care in the ICU allowing for careful monitoring of patients using well-defined algorithms to manage high and low glucose levels, but there may be multiple explanations for the reportedly low incidence of hypoglycemia in these studies. Among these, counterregulation (the ability to normalize glucose concentrations after insulin-induced hypoglycemia) may be intact in critically ill patients with type 2 diabetes or without diabetes; continuous infusion of glucose or nutrition along with insulin (through a glucose and insulin infusion as in the DIGAMI trial, a glucose and insulin and potassium infusion as in the stroke trial, and dextrose solutions and nutrition as in the Van den Berghe et al trial) may minimize the risk of hypoglycemia.[17,18] Alternatively, the recognition of adverse consequences of hypoglycemia (ie, neuroglycopenic symptoms and signs) may be hindered in critically ill patients.

Taken together, the existing data strongly suggest that the hyperglycemic milieu is a risk factor for adverse outcomes in acutely ill patients. Further research should focus on the optimal management of hyperglycemia in hospitalized patients and the effect of this on adverse outcomes.

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