Commentary

Hyperglycemia and outcomes in patients with sepsis

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van Vught and coworkers studied the relationship between admission glucose levels greater than 70 mg/dL and outcomes in critically ill patients with sepsis (1). This study included 987 patients; the distribution of admission glucose values measured in the time frame of 4 h before admission to 4 h after admission included 519 patients with euglycemia (71–140 mg/dL), 267 patients with mild hyperglycemia (140–199 mg/dL), and 201 patients with severe hyperglycemia (≥200 mg/dL). These glucose measurements were obtained early in the sepsis course and presumably reflect glucose regulation before treatment of infection and of elevated glucose levels. Patients with mild and severe hyperglycemia were older, had higher body mass indices, and had more chronic co-morbidity. In addition, 53.7% of patients with severe hyperglycemia had a history of diabetes. The proportion of patients with organ failure was similar in the three groups, but shock on ICU admission was significantly more frequent in patients admitted with normal glucose levels. Patients with severe hyperglycemia developed acute kidney injury and acute myocardial infarction more frequently while in the ICU. Multivariable Cox regression analysis demonstrated that patients with severe hyperglycemia had an increased risk for mortality by day 30 compared to patients with euglycemia (hazard ratio =1.66; 95% CI, 1.24–2.23). This adverse effect of severe hyperglycemia was present in both patients with and without diabetes. There appeared to be a complex interaction between glucose levels and lactate levels in this study. In the overall cohort and in patients with diabetes, hyperglycemia was associated with increased mortality after correction for the highest lactate value obtained during the first 24 h. However, hyperglycemia was not associated with increased mortality in patients without diabetes after adjustment for lactate. Patients with sepsis had increased acute phase protein responses and activation of cytokine networks, the vascular endothelium, and coagulation pathways. There was no increase in these levels suggesting unregulated cytokine production, and these responses were reduced or blunted in patients with both mild and severe hyperglycemia. This information on inflammatory responses is relevant to both host defense responses to infection and to dysregulated host defense responses and organ dysfunction associated with sepsis.

Not all studies have identified hyperglycemia as an independent predictor for mortality in patients with acute medical disorders. Green *et al.* studied 1,236 emergency department patients to determine the associations between hyperglycemia and hyperlactatemia with mortality (2). Hyperglycemia (>200 mg/dL) was associated with simultaneous hyperlactatemia, and hyperglycemia with concurrent hyperlactatemia (>4 mmol/L) was associated with increased mortality (OR =3.96; 95% CI, 2.01–7.79). However, hyperglycemia in the absence of elevated lactate levels was not associated with increased mortality (OR =0.78; 95% CI, 0.39–1.57). Kaukonen and associates analyzed 152,349 simultaneous measurements of glucose and lactate in critically ill patients (3). They used multivariable analysis to study the associations between different metrics of glucose and lactate with hospital mortality. Elevated glucose levels on day 1 of admission were associated with increased mortality. Elevated lactate levels were also associated with increased mortality. However, when both glucose and lactate were entered into multivariable regression models, all measures of hyperglycemia became insignificant in any association with hospital mortality. They concluded that there was no independent association between hyperglycemia and mortality after adjustment for lactate levels. Tiruvoipati *et al.* studied 297 patients admitted to an intensive care unit (4). Two hundred and four patients had stress hyperglycemia, defined as an average glucose value >6.9 mmol/L (124 mg/dL). The mean glucose level was

8.7 mmol/L (157 mg/dL) in patients with stress hyperglycemia. There were no significant differences in demographic characteristics or disease characteristics between patients with and without stress hyperglycemia. On logistic regression analysis, stress hyperglycemia was associated with reduced mortality (OR =0.42; 95% CI, 0.20–0.88), including a subgroup with septic shock (OR =0.31; 95% CI, 0.12–0.81). This unexpected result might be explained by improved cellular uptake of glucose when present at moderate levels and by their patient population which did not include patients with major trauma, or neurosurgical patients, or cardiac surgery patients.

All studies investigating the relationship between hyperglycemia and outcomes in patients with sepsis need to consider patient characteristics and co-morbidity at presentation, adverse events during the hospitalization, and, in particular, the presence or absence of diabetes prior to hospitalization (1). In addition, the duration of diabetes and the quality of outpatient management (HbA1c levels) prior to acute illness might be important factors in these patients. This information is likely available in larger prospective databases and allows for adjustment in statistical models which should reduce the possibility of spurious conclusions about glucose effects. However, we should not assume that the loss of statistical significance in a multivariable model indicates that hyperglycemia is unimportant in complex patients.

Multiple factors influence glucose levels in patients with sepsis. Sepsis stimulates gluconeogenesis using recycled pyruvate and lactate, using glycerol from mobilized fatty acids, and using glucogenic amino acids mobilized by proteolysis (5-7). Glycogenolysis can also increase glucose levels, and relative insulin resistance reduces glucose uptake in some organs and prevents insulin modulation of gluconeogenesis in the liver. However, glucose uptake in some tissues is increased through insulin independent glucose transporter, such as GLUT 1, 2, and 3. Multiple hormones associated with stress stimulate gluconeogenesis, and these include glucagon, epinephrine, and cortisol. Lactate production requires glycolysis and the production of pyruvate and then lactate. Increased lactate levels can occur when large fluxes of glucose exceed the capacity of mitochondria to take up pyruvate and when mitochondrial dysfunction impairs the uptake of pyruvate and its metabolism in the citric acid cycle (8). Consequently, the number and complexity of factors which influence glucose levels probably exceed simple interpretation. However, glucose levels reflect, in part, the degree of stress associated with an acute illness and indicate abnormal metabolic responses during acute illness. Lactate levels are potentially more easily interpreted since they should reflect pyruvate formation and mitochondrial function. However, lactate is also recycled into glucose in the liver and kidney, and lactate levels necessarily reflect formation and metabolism. Classifying patients according to glucose levels and lactate levels or according to glucose-lactate ratios might help identify patients with increased mortality in sepsis. In addition, this classification could provide a better understanding of the metabolic disturbances in a particular patient.

Other considerations in studies on outcomes associated with hyperglycemia must include direct effects of hyperglycemia independent of any metabolic classification. Hyperglycemia does have direct effects on the innate immune system, particularly on neutrophils (9). High glucose levels reduce phagocytosis and bacterial killing by neutrophils and reduce the formation of neutrophil extracellular traps which kill bacteria in the absence of ingestion by phagocytosis. Hyperglycemia also has important effects on micro vascular function which could result in increased permeability, effects on complement, and effects on cytokine production and the balance between inflammatory and anti-inflammatory cytokines (9). Hyperglycemia associated with increased glucose uptake in the cells can have direct toxic effects through glucotoxicity (10,11). High intracellular glucose levels stimulate the formation of reactive oxygen species which, in turn, can damage lipid membranes, nucleic acids, and proteins. Direct effects associated with hyperglycemia almost certainly would depend on the glucose level and duration of sustained hyperglycemia. Finally, the use of insulin can modulate host defense responses independent of its effect on glucose levels and needs to be considered in outcome studies (7,12).

Can the pathophysiologic basis for hyperglycemia in critically ill patients help explain the association or lack of association between hyperglycemia and mortality in these patients? Does hyperglycemia reflect an acute stress response in patients with sepsis and provide a single numerical measurement of this stress response? In this formulation patients with severe hyperglycemia have severe stress and have increased mortality. Does hyperglycemia serve as a better indicator of abnormal metabolic responses during stress than lactate levels (8)? What is the association between hyperglycemia and lactate levels? These considerations suggest that a model including these two factors might provide better prediction of outcomes. Alternatively, does hyperglycemia just reflect other co-morbidities in these patients? In this formulation hyperglycemia is not a critical illness stress indicator but

a marker for co-morbidity. In the van Vught study, the multivariate model included a modified SOFA score to adjust for comorbidity (1). Does hyperglycemia represent a risk factor for adverse events during hospitalization for acute illness and not function as a stress indicator or a marker for co-morbidity? In the van Vught study, patients with severe hyperglycemia developed acute kidney injury and myocardial infarction more frequently. The explanation for this effect is unclear in their study. Does hyperglycemia have direct effects on host defense responses which impair the control and clearance of infections? This consideration most likely involves innate immunity and neutrophils, vascular events, complement, and/or cytokines (9). Or does hyperglycemia cause direct tissue injury through glucotoxicity and increase adverse outcomes?

In summary, hyperglycemia occurs frequently in patients with sepsis. This may have a beneficial effect in some patients because high levels increase the diffusion gradient in tissues that may have an abnormal microvasculature related to sepsis. However, the main concern in most clinical studies is adverse effects secondary to hyperglycemia. These effects probably depend on the level of glucose in a particular patient, the time associated with high levels, and possibly the glucose variability (13). Hyperglycemia is closely associated with high lactate levels, and these lactate levels need to be considered in any analysis of the importance of hyperglycemia. Since the standard approach to the management of patients with sepsis now includes frequent lactate measurements, large clinical databases must exist which include information on these values in septic patients. Efforts to create a metabolic classification of patients with sepsis may improve our understanding of the pathophysiology in these patients and may help identify patients who need more attention to either glucose levels or lactate levels or both.

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Footnote

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