Glycemic Control and Critical Illness: Is the Kidney Involved?

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ABSTRACT
The pathophysiology, consequences, and management of hyperglycemia during critical illness is an important clinical issue. Uncontrolled hyperglycemia in this setting is associated with a variety of adverse events, including mortality. The kidneys have a major role in glucose and insulin metabolism, and emerging evidence suggests that they both are actively involved in the development, maintenance, and resolution of hyperglycemia. The development of acute kidney injury is also a risk in this setting. This article discusses potential approaches for efficient and effective management of hyperglycemia.


Effective management of hyperglycemia in critically ill patients has been a major topic of discussion since a landmark study demonstrated a significant reduction in mortality and morbidity in surgical patients who were treated with an intensive regimen to control blood glucose.1 Subsequent studies have highlighted the importance of hyperglycemia for adverse outcomes in various populations and proposed algorithms for glycemic control.2–4 However, achieving glycemic control is not easy, and additional questions have emerged.5,6 These include identifying potential mechanisms for the deleterious effects of hyperglycemia and the protective role of insulin in glycemic control.2,4 These include identifying potential mechanisms for the deleterious effects of hyperglycemia and the protective role of insulin in glycemic control.2,4 The risk for hypoglycemia has also prompted concerns that one must identify patients who are most likely to benefit from insulin therapy.9 Emerging evidence raises intriguing questions on the role of the kidney in this process and provides an opportunity to learn from these observations.

A key feature of hyperglycemia in critical illness is the development of insulin resistance coupled with alterations in glucose production and cellular glucose transport. Hepatic glucose production is increased through gluconeogenesis and glycogenolysis despite high levels of serum insulin that ordinarily suppress these pathways. Glucose utilization by cells normally occurs through facilitated uptake via glucose transporters (GLUT), which are widely distributed in tissues, including the kidney. Insulin-independent GLUT-1–mediated transport occurs in most tissues and accounts for basal glucose uptake, whereas expression and binding through GLUT-4 in skeletal muscle are regulated by insulin.8,10

Normally, hyperglycemia leads cells to internalize GLUT proteins to protect themselves from glucose overloading. However, in critical illness, membrane expression of GLUT-1, GLUT-2, and GLUT-3 proteins is upregulated and allows glucose to enter cells more in proportion to extracellular glucose levels. This contributes to glucose overload in several tissues, including brain neurons, hepatocytes, endothelial cells, and renal tubules. These events are associated with various cytokines (TNF-α and IL-6), hormones (cortisol, catecholamines, and growth hormone), and other molecules (vascular endothelial growth factor and TGF) that are also upregulated in multi-organ failure.11 Several additional pathways are also invoked, including cytokine-induced nitric oxide production, oxidative stress and hyperlipidemia. In this complicated series of events, what role does the kidney play?

A large multicenter study of patients with acute kidney injury (AKI) found that insulin resistance is common and the degree of hyperglycemia correlated with mortality.12 Mean insulin concentrations and mean homeostasis model of insulin resistance levels were significantly higher and IGF binding protein-3 concentrations were significantly lower among nonsurvivors compared with survivors.13 Additional data from the same cohort point to a much higher prevalence of elevated pro- and counterinflammatory cytokines, cellular paralysis of cytokine production, and increased markers of oxidative stress that all correlate with increased mortality.14–16 Although the development of AKI is associated with severe metabolic derangements, we

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have no clear evidence for a causal relationship.

The kidney also plays an important role in glucose homeostasis. Renal tubular handling of glucose is mediated by the facilitative GLUT proteins and the Na+/glucose co-transporter (SGLT) family. In humans, renal glucose production contributes approximately 25% to systemic glucose production, whereas renal glucose uptake accounts for 20% of systemic glucose removal. Because glucose homeostasis in the kidney is regulated by insulin, loss of kidney metabolic function could account for a component of insulin resistance as a result of loss of a major target organ for insulin action. Uremia is also associated with decreased hepatic and peripheral glucose uptake and a reduction in peripheral tissue glucose transporters. Hypertriglyceridemia, hyperglycemia, and hyperinsulinemia were seen in an animal model of cisplatin nephrotoxicity, and biochemical studies demonstrated the accumulation of nonesterified fatty acids, and triglycerides in serum, urine, and kidney tissue despite increased levels of plasma insulin. A reduced plasma glucose level, impaired renal tissue perfusion and GFR, and increased fractional glucose excretion were associated with decreased expression of SGLT2, SGLT3, and GLUT2 in an LPS model of sepsis, and similar findings were observed after application of TNF-α, IL-1β, IL-6, or IFN-γ.

Insulin is also metabolized by the kidney, and reduced renal function prolongs the half-life of insulin and can contribute to hypoglycemic events. One of the major risk factors for development of hypoglycemia in the intensive care unit (ICU) was the presence of preexisting renal dysfunction and the need for renal replacement therapy. Multiple lines of evidence in human and animal studies point to the importance of the kidney in glucose homeostasis and as a potential contributor to insulin resistance, suggesting that it is an active participant in these metabolic derangements during critical illness.

In the absence of diabetes, mild to moderate elevations of glucose have not been associated with alterations in kidney function. Data from the glycemic control studies (Table 1), however, suggest otherwise and support the need for reappraisal. The Leuven study demonstrated that maintaining blood glucose levels <110 mg/dl reduced the onset of new renal failure from 12.3 to 9% (P = 0.04) and need for dialysis by 41%. Whereas the lowered blood glucose level was related to reduced mortality and other complications, the insulin dosage was an independent determinant for prevention of AKI. Two large intervention studies in medical and surgical ICU patients confirmed a similar association and found that the development of newly acquired AKI decreased by 75% and 45%, respectively. In a large observational study, patients who did and did not have diabetes and required glycemic control had more infections, anemia, and AKI (11 and 7 versus 4%; P < 0.001) compared with control subjects. Additional observational studies from different populations suggest a linkage of hyperglycemia and the metabolic syndrome on the development of AKI. Most of these studies used a doubling of creatinine or a creatinine level >2.5 mg/dl as a criterion for AKI; however, a more sensitive criterion (0.5 mg/dl creatinine change) would likely increase the incidence of AKI. Whether these associations are simply a consequence of the deranged metabolic milieu that accompanies critical illness or there is a direct effect of hyperglycemia and insulin resistance on the kidney still needs more evaluation.

The mechanisms for the insulin resistance seen in chronic metabolic syndrome may mediate renal injury through several different pathways (Figure 1). Are these mechanisms operative in AKI, and, if so, what is the time course to develop renal injury? Findings from a wide variety of models of AKI, including ischemia/reperfusion, cisplatin, endotoxemia, glomerulonephritis, and ureteral obstruction, provide support for a direct contribution of hyperglycemia and insulin resistance to renal injury. Accumulation of nonesterified fatty acids seems to be a major factor contributing to mitochondrial dysfunction, influencing cellular recovery in renal tubular cells. These events operate through a variety of molecular and signaling pathways. On the basis of these AKI models, it seems that the same pathways may influence critically ill patients, although experimental events as described here seem accelerated in contrast to the longer duration required for chronic insulin resistance to produce AKI (Figure 2). A likely scenario is that stress-related hyperglycemia induces compensatory responses in the kidney with resulting glycosuria. However, if the primary illness is not controlled, then the consequences of hyperglycemia in the kidney seem to be a major factor contributing to and in whom glucose levels were kept at <110 mg/dl. This would fit well with the notion that critical illness evolves over time and there may be recruitment of various deteriorating organs as additional pathways are brought to bear. The kidney may have a dual role in conditioning the response to initial injury through preexisting or concurrent alterations in renal function and may also be a target of the altered metabolic pathways.

What are the lessons learned? Although several pieces of the puzzle linking hyperglycemia and kidney function are still missing, there is enough evidence now to suggest that the kidneys are active in the process and a target for new injury. On the basis of these conclusions, hyperglycemia should be considered a major risk factor for AKI in the ICU and should prompt specific measures to be instituted as follows:

First, clinicians should seek out a history of hyperglycemia as part of the evaluation of critically ill patients who are at risk or develop AKI and institute preventive and therapeutic measures. A variety of therapies may contribute directly or indirectly to the onset of hyperglycemia and should be avoided (Table 2). For instance, it is not uncommon to use 5%
dextrose solutions to replace free water, and some centers still use dextrose-containing solutions in peritoneal dialysis or in the infusate for continuous renal replacement therapy. Dialysate solutions for intermittent hemodialysis also contain variable amounts of glucose and contribute to the dextrose load. 32–34

Second, when hyperglycemia exists, early intervention to achieve and maintain glycemic control should be initiated. Several different regimens have been described; however, none specifically considers altered renal function, particularly with respect to the target range for blood glucose. 35,36 Given the higher likelihood of hypoglycemia with reduced GFR, it maybe prudent to select a conservative target glucose of 100 to 149 mg/dl rather than an aggressive target of 80 to 109 mg/dl. 37 Dynamic scales should be used to adjust insulin delivery rates on the basis of 1- to 4-h glucose monitoring. Insulin regimens should be combined with simultaneous enteral feeding to minimize hypoglycemia. 36,38 Renal function should be monitored daily and a urinalysis performed for glycosuria, proteinuria, cells, and casts.

Third, altered renal function should be recognized as a risk factor for insulin resistance and its downstream effects. An estimated or measured GFR should be a part of the initial evaluation of ICU patients. Patients with decreased GFR should be considered a special subset for risk for glycemic control and hypoglycemia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (No. of Patients)</th>
<th>Design</th>
<th>Renal Parameters</th>
<th>Findings</th>
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<td>Van Den Berghe et al., 2001 32</td>
<td>Surgical ICU (62% after cardiac surgery) (1548)</td>
<td>RCT: Intensive glucose control to 80 to 110 mg/dl versus control group target 190 to 200 mg/dl</td>
<td>Peak plasma creatinine &gt; 2.5 mg/dl, peak BUN &gt; 54 mg/dl; need for RRT (IHD or CRRT)</td>
<td>Intensive insulin group had 42% reduction in risk for death and newly developed kidney failure requiring dialysis by 41%, peak serum creatinine 12.3 versus 9%, peak BUN 11.2 versus 7.7% in controls versus intensive treatment. Respectively, insulin dosage was an independent determinant of ARF.</td>
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<td>Hospital mortality in the protocol group decreased 29%, development of new renal insufficiency decreased 75%</td>
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<td>Holm et al., 2004 34</td>
<td>Burns &gt; 25% (37)</td>
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<td>Case-control study</td>
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<td>No significant difference in mortality; reduction in newly acquired kidney injury (8.9 to 5.9%, P = 0.04); serum creatinine change &gt; 2× normal (12.6 versus 8.3%), and peak creatinine &gt; 2.5 mg/dl (39.4 versus 32.5%) in controls versus intensive insulin-treated groups; use of dialysis in patients who did not require dialysis before admission to the ICU was not significantly reduced (22.7% [control] versus 20.8% [intensive-treatment group], P = 0.5); maximum benefit in patients in ICU &gt; 3 d</td>
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Note: AMI, acute myocardial infarction; ARF, acute renal failure; BUN, blood urea nitrogen; CI, confidence interval; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IHD, intermittent hemodialysis; OR, odds ratio; RCT, randomized, controlled trial; RRT, renal replacement therapy; TPN, total parenteral nutrition.

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Table 1. Evidence for hyperglycemia in critical illness as a risk factor for acute kidney injury

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CLINICAL COMMENTARY

Figure 1. Mechanisms by which insulin resistance can contribute to renal injury. Adapted from Sarafadis et al.,29 with permission from S. Karger AG, Basel, Switzerland.

In addition, the effect of reduced GFR on enhancing risk for drug-induced hyperglycemia and, to a lesser extent, hypoglycemia, particularly with antibiotics such as gatifloxacin, should be recognized.29 Similar adjustments may be required when calcineurin inhibitors and steroids are used in delayed graft function after renal transplants.41 When dialysis is instituted, further adjustments in insulin dosing and more frequent glucose monitoring may be required. One study evaluating risk factors for hypoglycemia found a strong relationship with development and resolution of hyperglycemia in the critically ill patient. It is time we recognized the interdependence of various organs and the expanded role of the kidney in modulating the response to catastrophic illness.

Fourth, future studies should focus on assessing hyperglycemia or the metabolic syndrome as risks for AKI to ascertain the mechanisms and pathways contributing to renal injury. Patients with diabetes may have a different threshold for hyperglycemic injury, although the relationship to preexisting renal disease is unclear.7 The influence of a reduced GFR and dialysis on glucose and insulin levels needs to be explored further. Two large studies evaluating strategies for glycemic control are under way and could offer information in this regard.6

Current evidence suggests that the kidney is intimately involved in the development and resolution of hyperglycemia in the critically ill patient. It is time we recognized the interdependence of various organs and the expanded role of the kidney in modulating the response to catastrophic illness.

Table 2. Modifiable factors contributing to hyper- and hypoglycemia in critically ill patients with renal dysfunction

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<th>Dialysis Related</th>
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</thead>
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<td>Hyperglycemia</td>
<td>Use of 5% dextrose solutions as a source of free water for hypernatremia, TPN and enteral solutions, Antibiotics (fluoroquinolones [e.g., gatifloxacin])</td>
<td>Dextrose-containing dialysate (e.g., PD solutions for CRRT), Dextrose in anticoagulant (e.g., ACDA for citrate anticoagulant), 5% dextrose as component of replacement fluid in CRRT to manage hypernatremia, Bicarbonate-based CRRT, Insulin dosage adjustments when dialysis stopped</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Oral hypoglycemics, Insulin dosage, type and route of administration, Antibiotics (gatifloxacin), Calcineurin inhibitors and steroids</td>
<td></td>
</tr>
</tbody>
</table>

*ACDA, anticoagulant citrate dextrose solution, formula A; PD, peritoneal dialysis.

DISCLOSURES

None.

REFERENCES