NARRATIVE REVIEW

Is There a Role for Intensive Insulin Therapy in Patients With Kidney Disease?

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There is increasing evidence for the benefit of intensive insulin therapy in maintaining near-normoglycemia in patients without diabetes with severe acute illness. Morbidity and mortality have both improved, with decreased episodes of sepsis, acute kidney injury, transfusion requirements, and post–intensive care complications. The metabolic mayhem of severe acute illness has many parallels with those induced by kidney failure itself, and patients with kidney failure are at increased risk from many of the complications potentially improved by insulin therapy. We reviewed the potential benefits of intensive insulin therapy and examined the published trials for data directly applicable to patients with kidney failure. There are no trials directly answering the question and no specific analysis of patients with kidney disease in published studies. We extracted pertinent data regarding patients with impaired renal function from the reported trials, identified parallels between patients with kidney injury and other severe illnesses, and suggest possible future studies. We hypothesize that intensive insulin therapy has a role outside the intensive care setting and, in particular, a role for patients with severe acute illness and kidney failure, whether acute or chronic.

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Patients with acute or chronic kidney failure have high rates of morbidity and mortality. Across the United Kingdom, 320,000 bed-days are used by hemodialysis patients per annum, with an overall 5-year survival rate of patients on renal replacement therapy of 43%. Kidney failure, both acute and chronic, has much in common with critical illness. Parallels in patients with acute kidney injury (AKI) are obvious, and patients often have renal injury as part of multiorgan failure. Intercurrent illness on the background of chronic kidney disease (CKD) also has many parallels, with high mortality, metabolic disturbance, and cardiovascular instability. During the last few years, tight control of blood glucose levels with intensive insulin therapy was shown to improve outcomes in critically ill patients regardless of whether diabetes previously was diagnosed.[1-4] It is believed that insulin to some extent reverses the detrimental metabolic derangements that occur when patients are severely unwell. Intensive insulin therapy is now a widely accepted practice on general intensive care units (ICUs). Given the importance of this intervention in intensive care, we hypothesize that intensive insulin therapy also may have a role outside the intensive care setting and, in particular, for patients with severe acute illness and kidney failure, whether acute or chronic. This might include hospitalized patients with AKI of any sort, from acute tubular necrosis, rapidly progressive glomerulonephritis, or obstructive nephropathy, and also patients with CKD and such severe acute intercurrent illnesses as pneumonia, sepsis, pulmonary edema, acute coronary syndromes, and peritonitis, among others.

Intensive insulin therapy is a simple and inexpensive intervention that has the potential to improve clinical outcome in severe illness in patients with kidney disease, as it has done in intensive care, and it can be initiated easily on selected wards, although it requires training, close monitoring, and intensive nursing input.[5] It is not appropriate in outpatient hemodialysis settings. In this review, we explore the pathophysiological

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characteristics of critical illness with respect to the role of intensive insulin therapy, parallels in renal failure, and available evidence for the use of intensive insulin therapy in patients with established kidney injury or AKI.

AKI frequently is associated with a number of other organ system failures. A recent study estimated an annual incidence of AKI of 200 per million population.[6] AKI treated in the ICU is associated with mortality rate of 64% to 79%.[7,8] The most common precipitating factor is sepsis, at least partly causative in 69% of cases. Other common causes of AKI are surgery, hypotension, hypovolemia, urinary tract obstruction, pancreatitis, nephrotoxic drugs, and gastrointestinal hemorrhage. Survival of patients with AKI requiring renal replacement therapy is poor; 71% of patients with AKI or acute-on-chronic kidney injury died within 90 days of starting renal replacement therapy, with a median survival of only 8 days.[6]

Patients with CKD also have high levels of mortality and morbidity. Five-year survival rates of dialysis patients are 64% for patients younger than 65 years and 14.5% for older patients, with cardiac disease and infection accounting for 52% and 20% of deaths, respectively. At any 1 time, 5% of hemodialysis patients are hospital inpatients.

CRITICALLY ILL PATIENTS HAVE DISTURBED LIPID AND GLUCOSE METABOLISM

The altered metabolism found in patients with critical illness results in insulin resistance, abnormal serum lipid profile, increased protein turnover, negative nitrogen balance, proteolysis of skeletal muscle, systemic inflammation, and, ultimately, multiple organ failure.[9-11] Hormonal changes in response to stress[12] combined with the side effects of treatments also contribute to this "metabolic mayhem."

Hyperglycemia is common in critically ill patients, even those who did not previously have diabetes,[10] and has been reported in the literature for almost 150 years. It is well known that any type of severe acute illness or injury results in hyperglycemia and its associated widespread metabolic and immunologic disturbances.[13] Increased levels of glucagon, cortisol, and growth hormone, released in response to stress, enhance hepatic gluconeogenesis and increase blood glucose levels.[14] The increased endogenous and exogenous catecholamine levels found in patients with critical illness inhibit insulin secretion from pancreatic β cells and also increase hepatic glycogenolysis. Inflammatory cytokines, particularly interleukin 1, interleukin 6, and tumor necrosis factor, are found at high levels in patients with acute illness and alter insulin receptor signaling to stimulate the release of hormones that promote hyperglycemia.[13,15] Hyperglycemia is also caused by excessive dextrose administration, high-calorie feeding, parenteral nutrition, and commonly used medications such as corticosteroids, catecholamines, and thiazide diuretics.

It is well documented that the liver, heart, skeletal muscle, and adipose tissue become less responsive to insulin during critical illness, but the molecular basis for this is not clear. In the liver, expression of some hepatic insulin receptors is decreased[10] and insulin-stimulated glucose uptake in heart and skeletal muscle is impaired.[16] Other molecules, such as angiotensin II, which increases plasma concentrations in critical illness, exert anti-insulin effects.[17]

The abnormal lipid profile seen in patients with critical illness is characterized by increased triglyceride and very low-density lipoprotein (VLDL) levels, with a decrease in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL).[18] The cause of the change in lipid profile is not clear, and data are limited about its effects. One retrospective study described a U-shaped relationship between serum cholesterol level and mortality.[19] Increased free fatty acid flux toward the liver may lead to hepatic steatosis, and patients with kidney failure have a lipid profile similar to that in patients with critical illness.

IS HYPERGLYCEMIA DETRIMENTAL IN CRITICAL ILLNESS?

Metabolic changes that occur in patients with critical illness are now generally believed to be maladaptive. In the past, hyperglycemia was considered beneficial, providing glucose for wound healing, brain cells, and red blood cells, all of which increase glucose uptake during critical illness. However, more recently, hyperglycemia was associated independently with adverse outcome in patients with a range of acute diseases. This included chronic obstructive pulmo-