CHAPTER 215

Management of Patients with Diabetes in the Intensive Care Unit

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OBJECTIVES

This chapter will:

1. Describe the epidemiology of diabetic kidney disease and the burden of illness in the intensive care unit (ICU) setting.
2. Illustrate the spectrum of renal disease observed in patients with diabetes in the ICU.
3. Describe the metabolic abnormalities observed in patients with diabetes in the ICU.
4. Review the evolution of glycemic targets in the ICU.
5. Recommend treatment strategies for patients with diabetes in the ICU.

WHAT IS KNOWN AND WHAT IS NOT KNOWN

Despite recognition of diabetes mellitus (DM) as a risk factor for acute kidney injury (AKI), the inclusion of DM in stratifying patients within large databases is not consistent. In reviewing several papers describing the risk, injury, failure, loss, and end-stage renal disease (RIFLE) and Acute Physiology And Chronic Health Evaluation (APACHE) scores and the use of new biomarkers for AKI, we were surprised to find that DM was not identified overtly in the demographics of any of the published studies.[1–4] Nonetheless, in other studies, DM is a well-recognized risk factor for AKI, and the coexistence of DM in the critical care population raises unique management challenges for clinicians. This chapter reviews key issues related to the incidence, prevalence, and care of patients with diabetes in critical care settings.

EPIDEMIOLOGY AND BURDEN OF ILLNESS

Diabetes is a prevalent metabolic disorder estimated to affect more than 340 million people worldwide.[5] The United States alone had 29.1 million people living with diabetes in 2012, comprising 9.9% of the total population. This number still is expected to rise with one study claiming it may be possible that one in three adults living in the United States will be diagnosed with diabetes by 2050.[6,7] This high prevalence and increasing incidence are important in that these patients are at high risk for AKI in a multitude of settings.

Patients with diabetes frequently require hospital admission for diabetic and nondiabetic complications. In general, it has been reported that patients with diabetes have a threefold greater chance of hospitalization for all causes compared with their nondiabetic counterparts.[8,9] Despite focus on optimal diabetic management, there is ongoing evidence that complications including myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, AKI, and infections will continue to increase.[10] Diabetics with evidence of kidney disease (proteinuria, abnormal kidney function) are at greater risk of AKI than those without renal involvement. Retinopathy, neuropathy, coronary disease, and peripheral vascular disease are more prevalent in patients with nephropathy.[11] Patients with diabetes may require intensive care, most commonly for treatment of conditions other than diabetes. Once hospitalized, patients with diabetes have a longer duration of stay than nondiabetics with an increased risk for complications and increased mortality.[12,13] Therefore efficient and effective treatment for these patients is increasingly important from a patient outcome and a cost perspective.

DIABETIC KIDNEY DISEASE: KIDNEYS AT RISK

Diabetic nephropathy is common both in type 1 and type 2 DM. In type 1 diabetes, earlier literature reported a 16% chance of developing end-stage renal disease within 30 years after the initial diagnosis.[14,15] Historically, patients with type 2 diabetes were believed to have a better renal prognosis, but recent epidemiologic studies have suggested that the renal risk of a patient with type 2 DM is similar to that of a patient with type 1 diabetes.[16] Type 2 diabetes, which is 10 to 15 times more common than type 1, is the leading cause of end-stage renal disease in the Western world.[17,18]

Hyperfiltration: Missing Those at Risk

The initial stages of diabetic nephropathy are characterized by hyperfiltration and renal hypertrophy. Glomerular filtration rates (GFRs) during these stages may be 25% to 50% greater than normal. This hyperfiltration may be more pronounced in patients with type 1 diabetes, with GFRs often exceeding 150 mL/min; the appearance of supranormal GFR (or very low creatinine values) should raise suspicion of hyperfiltration. Patients who develop glomerular hyperfiltration appear to be at increased risk for progressive diabetic renal disease.[19] Because many patients present to the intensive care unit (ICU) in these stages of diabetic renal disease, clinicians must be vigilant, recognizing that, for many patients with diabetes, a normal creatinine or GFR may represent hyperfiltration or early kidney disease. Corroboration with urinalysis (presence of proteinuria) and previous laboratory tests is recommended.

Given the impaired kidney autoregulation, the often overwhelming burden of illness, and the susceptibility to damage, the current literature suggests that strict glycemic and blood pressure control, as well as minimizing nephrotoxin exposure, are key strategies to reduce AKI in acute settings.

Acute Kidney Injury

The prevention of AKI in critically ill patients is crucial, because renal failure in the ICU setting repeatedly has been identified as an independent predictor of mortality.[20,21] Patients with diabetes are at increased risk of AKI in the ICU because of several factors, including extracellular fluid volume contraction, diabetic ketoacidosis, nonketotic hyperosmolar coma, other kidney diseases, papillary necrosis, and obstruction. In addition, many of these patients are taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers before their ICU admission, which may be a factor in their AKI.

Patients with diabetes who are nephrotic, and therefore extracellular fluid volume contracted, are at increased risk of prerenal insults and acute tubular necrosis. Acute diabetic complications such as diabetic ketoacidosis and nonketotic hyperosmolar coma, which are characterized by profound extracellular fluid volume contraction and absolute or relative insulin lack, can lead to AKI. Patients with diabetic nephropathy are also at increased risk of contrast-induced nephropathy because of a number of factors, most of which were listed earlier. Cholesterol embolization also should be considered in a patient with AKI, because many patients with diabetes also have a significant atherosclerotic burden.

In the case of acute changes in kidney function in a patient with diabetes, nondiabetic glomerular diseases also must be considered. Clinical findings of hematuria, changes in proteinuria, and blood pressure control have been described in patients with a nondiabetic primary glomerular disease and have been well documented in patients with diabetes. Membranous nephropathy generally has been considered the most commonly associated nephropathy.[22] If there is an acute deterioration in renal function, a rapidly progressing glomerulonephritis should be considered. Nondiabetic glomerular disease should be considered in the patient with diabetes with AKI if the patient has a short duration of diabetes, no previous documented proteinuria, no retinopathy, red blood cells on urinalysis, and rapidly deteriorating renal function.

Urinary Tract Infections

Urinary tract infections are more common in patients with diabetes, especially those infections caused by gram-negative organisms; many of these infections are documented in the absence of symptoms.[23] Complications such as acute pyelonephritis with associated perinephric abscesses and emphysematous pyelonephritis are also more common in patients with diabetes. Renal papillary necrosis, caused by low flow states and ischemia-induced sloughing of the papilla, is also common in long-standing diabetes and is described in the setting of urinary tract infection or infection more commonly.[24] Although early treatment of urinary tract infections has decreased the incidence of this complication, it still should be considered in the patient with diabetes with rapidly progressing acute renal failure.

Progressive Diabetic Renal Disease

Patients with diabetes may have progression of their underlying kidney disease during their hospitalization. Alternatively, an episode of AKI superimposed on preexisting chronic kidney disease can leave patients with further reduced kidney function when they leave the ICU or hospital. It is recognized more frequently that minimizing AKI in these patients is important to reduce the long-term morbidity related to the accelerated progression of chronic kidney disease, which can be exacerbated by episodic AKI.

Metabolic Acidosis

Patients with diabetes in the ICU often have or develop metabolic acidosis, which may be related to the acute illness requiring ICU admission (e.g., lactic acidosis secondary to decreased perfusion) or, on occasion, may be more readily attributable to diabetes. Causes related directly to the diabetic state include preexisting renal tubular acidosis (RTA), an acute deterioration of diabetic control, and a drug-induced disorder such as metformin ingestion.

Drug-Induced Acidosis (Biguanides)

Oral hypoglycemic treatment with metformin (and previously phenformin) has been associated with the development of type B lactic acidosis in a subgroup of patients.[25,26] Risk factors including impaired kidney function (serum creatinine >132 μmol/L), liver disease, congestive heart failure, and excessive alcohol consumption have been reported. Importantly, most cases occur in the context of rapid change in kidney function, without concomitant adjustment of this renally excreted medication. Patients taking metformin who develop a severe illness requiring ICU admission (e.g., shock), in combination with abrupt reductions of kidney function, are at even greater risk of developing severe lactic acidosis.

Metformin is associated with lactic acidosis because of interference with pyruvate dehydrogenase function and subsequent decrease in lactate consumption. In patients with rapid reduction of kidney function, reduced excretion and subsequent increase in serum lactate levels cause the acidosis, which can be profound. A recent Cochrane database systematic review evaluated all prospective and observational cohort studies from 1966 to August 2005 that evaluated patients with type 2 diabetes treated with metformin compared with another hypoglycemic agent or placebo.[27] This review of 206 trials, representing 47,846 patient-years of metformin use, documented no cases of fatal or nonfatal lactic acidosis. In addition, no difference in lactate levels was found in groups treated with metformin versus non-metformin. The authors concluded that, under study conditions, metformin is not associated with an increased risk of lactic acidosis compared with other antihyperglycemic treatments. Nonetheless, it is the risk of AKI that more likely predicts the risk of metformin-induced metabolic acidosis, not the use of the drug.

Although not causative, the permissive impact of metformin use on diabetic outcomes raises a number of questions. The number of patients with diabetes treated with metformin continues to rise, and many patients still may be prescribed metformin despite reduced kidney function.[28] Cases of patients with profound lactic acidosis related to metformin use continue to be reported.[29]

Treatment of metformin-associated lactic acidosis includes supportive therapy and hemodialysis, if necessary. Conventional intermittent hemodialysis and continuous venovenous hemodiafiltration (CVVHDF) have been used with success.[29,30]

Unique Problems: Type 4 Renal Tubular Acidosis

A subset of patients with diabetes have an underlying type 4 renal tubular acidosis (RTA) manifested by impaired tubular secretion of hydrogen ion and potassium. This results in hyperchloremic acidosis with hyperkalemia. The serum bicarbonate level in this condition is low (average, approximately 18 mEq/L). The causes of this RTA are multifactorial but include interstitial fibrosis associated with progressive decline in kidney function. A few patients with diabetes with normal kidney function also have this RTA.[31] Patients with diabetes with this underlying disorder may present with a more profound acidosis than what could be explained on clinical circumstances alone. However, an intercurrent illness requiring ICU admission may unmask or even exacerbate the clinical picture. It is important to recognize this preexisting disorder (chronic metabolic acidosis, compensated), because it may affect a patient's response to therapy for these electrolyte abnormalities, and it may change treatment strategies.

Mixed Disorders

In addition to preexisting RTA and metformin-induced lactic acidosis, patients with diabetes may be acidotic for a number of other reasons. Diabetic ketoacidosis is a common cause of severe anion-gap acidosis, often requiring ICU admission for correction of the severe volume depletion and metabolic abnormalities that accompany the lack of insulin. A moderate degree of lactic acidosis, in addition to the recognized ketoacidosis, is also observed in some patients,[32,33] potentially because of the severe hypovolemia.

TREATMENT

General Principles

The principles of managing diabetes in the ICU setting have evolved. Recent guidelines suggest targeting a blood glucose level between 7.8 and 10 mmol/L (140 and 180 mg/dL) for the majority of patients, whereas in select situations (i.e., ICU centers with extensive experience, cardiac surgical patients, patients with stable glycemic control without hypoglycemia), modestly lower glucose targets may be preferred. Targeting blood glucose below 6.1 mmol/L (<100 mg/dL) is not recommended in ICU patients.[34]

In addition, to minimize the risk of AKI, prompt recognition of patients with diabetes who have or are at risk of having diabetic kidney disease is also important. Overreliance on the serum creatinine concentration is problematic because of the issues mentioned earlier regarding hyperfiltration, and the utility of a urinalysis should be emphasized in the evaluation of these patients.

Avoidance of nephrotoxins (e.g., aminoglycosides), nonsteroidal antiinflammatory drugs, and other drugs in the ICU and use of intravenous contrast only if no alternatives are available and with appropriate renal protection are important measures to reduce the incidence and subsequent morbidity of diabetic AKI.

Glycemic Control in Acute Care Settings

Patients with acute illness often have hyperglycemia and insulin resistance. This is observed even in patients without preexisting diabetes.[35] A large body of literature has identified a correlation between hyperglycemia in critically ill patients and poor clinical outcomes. The mechanisms responsible for the detrimental effects are not completely understood; however, associations with impaired neutrophil granulocyte functioning, proinflammatory cytokines, and reactive oxygen species have been suggested that may result in direct cellular damage with vascular and immune dysfunction.[36–41] Adverse effects of hyperglycemia include but are not limited to fluid and electrolyte shifts, decreased wound healing, immune dysfunction, and endothelial dysfunction.[42] A randomized trial of 1548 patients in a surgical ICU initially set the stage for intensive glucose control (target glucose concentration, 4.4 to 6.1 mmol/L) as it demonstrated a 42% lower mortality rate (4.6% vs. 8%; $p < .04$) compared with standard care (target glucose concentration 10–11.1 mmol/L).[43] Notably, the intensive treatment arm also required significantly less dialysis. Following similar protocol, the study was repeated in medical ICU patients and showed similar benefit to intensive glycemic control after 3 days of insulin therapy in this cohort of patients as well.[44] When combined, these two studies identified positive outcomes on morbidity and mortality; therefore glycemic targets of 4.4 to 6.1 mmol/L were suggested in the ICU setting. However, recent, well-designed randomized controlled trials and meta-analyses have identified that intensive glucose lowering significantly increases the risk of severe hypoglycemia.[45–48] These studies unanimously also have failed to reproduce the improvements in clinical outcomes that were previously suggested.[45–49] A large multicenter, international trial that randomized medical and surgical ICU patients to tight glycemic control (4.4–6.1 mmol/L) versus conventional glycemic control (7.8–10 mmol/L) did not find a difference in mortality outcomes between the two groups.[50]

The lack of benefit in intensive glucose lowering was demonstrated further by a trial of more than 6000 subjects randomized to conventional glycemic control (<10 mmol/L) versus intensive glycemic control (4.5–6 mmol/L).[49] There was no difference in hospital mortality reported; however, an increased mortality at 90 days of follow-up was seen (24.9% vs. 27.5%, $p = .02$) in patients subjected to intensive glycemic control. After subsequent analysis, it was determined that a significantly higher incidence of hypoglycemia was seen in the patients subjected to intense insulin therapy (6.8% vs. 0.5%). Hypoglycemia is a common side effect of treatment in all types of diabetes and a major challenge to identify in the critically ill because signs and symptoms of hypoglycemia in this population may be masked. The development of hypoglycemia is associated with poor hospital outcomes.[49–57] A study looking at patients with diabetes admitted to a mixed medical-surgical ICU found that those with inpatient hypoglycemia had a 66% increased risk of death within 1 year and spent 2.8 days longer in hospital. Odds ratio for mortality associated with one or more episodes of hypoglycemia was 2.28 (95% CI, 1.41–3.70, $P = .0008$).[58] Patients with hyperglycemia in the critical care setting require treatment; however, there is a lack of evidence demonstrating an ideal protocol/algorithm for management. Therapy should be based on

institution-ICU resources such as trained nursing staff. A variety of intravenous infusion protocols have shown effectiveness in achieving glycemic control with low rates of hypoglycemic events.[38,59–62] A protocol should allow for flexible blood glucose targets, modified based on the patient's clinical situation with clear instructions regarding the threshold to initiate and modify therapy. When a patient is identified as having hyperglycemia in the critical care setting (blood glucose levels above 10 mmol/L), intravenous insulin infusions generally are preferred to subcutaneous injections. If a patient required insulin before admission, then a basal level of insulin must be maintained, especially if the patient is prone to ketosis. Every attempt must be made to avoid hypoglycemia. Once a patient leaves the ICU, follow-up of glycemic control is important, especially if the patient was not known previously to be diabetic.

CONCLUSION

The incidence and prevalence of DM continue to increase worldwide, and the number of patients who have diabetic kidney disease, or who are at risk for severe illness that may precipitate AKI, also will continue to rise. Patients with diabetes often require hospital admission, and a subset require critical care for diabetic complications (diabetic ketoacidosis and hyperosmolar coma) and, more commonly, nondiabetic cardiac, vascular, and infectious conditions. Many patients with diabetes are at increased risk of AKI, for a number of reasons, including underrecognition of the problem because of an overreliance on the serum creatinine measurement and no review of urinalyses, hypovolemia resulting from osmotic diuresis, and diarrhea.

Early identification of at-risk individuals, avoidance of nephrotoxins, and prompt treatment are crucial to attenuate the increase in short- and long-term morbidity and mortality associated with AKI in the ICU. Future studies of AKI always should include diabetes in their stratification systems, given the importance and uniqueness of this group of patients.

Key Points

1. The incidence and prevalence of diabetes mellitus are rising.
2. Diabetic nephropathy remains a leading cause of end-stage renal disease. Patients with diabetes often require critical care admission for diabetic and nondiabetic complications.
3. Patients with diabetes are at substantial risk of acute kidney injury in the intensive care unit, and avoidance of nephrotoxins should be stressed in this population.
4. Metabolic acidosis is common in patients with diabetes. Specific causes include preexisting renal tubular acidosis, drug-induced disorders, and decompensated diabetes.
5. Intensive insulin therapy to treat hyperglycemia results in an increased risk of hypoglycemia which is associated with poor outcomes.

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