Diabetic Ketoacidosis in Patients with End-stage Kidney Disease: A Review

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ABSTRACT

Diabetes mellitus is a highly prevalent disease. Chronic kidney disease is one of its chronic complications, and diabetic ketoacidosis is one of the most dreaded acute complications. The increasing prevalence of diabetes mellitus and renal failure has resulted in physicians increasingly encountering diabetic ketoacidosis in this complicated subgroup of patients. This review discusses the pathophysiologic understanding of diabetic ketoacidosis in patients with renal failure, its varying clinical presentation, and management and prevention. We have also highlighted the role of patient weight and proximity to dialysis as tools to assess and manage fluid status in this challenging group of patients.

Diabetes mellitus is a major cause of end-stage kidney disease worldwide.[1,2] Patients with type 1 diabetes mellitus form a minority of those requiring dialysis. Encouragingly, several studies from various parts of the world have confirmed a declining rate of end-stage kidney disease in patients with type 1 and type 2 diabetes mellitus.[3–5] Despite this declining trend, the burden of end-stage kidney disease due to diabetes mellitus remains high.[6–9] Glucose metabolism is significantly affected by the decline in kidney function. Insulin degradation is reduced, and gluconeogenesis by the kidney is impaired in chronic kidney disease. These factors, combined with decreasing appetite due to uremia, result in an overall decline in blood glucose levels in some patients with type 2 diabetes mellitus. These patients, however, do not become 'immune' to the usual complications of the disease.

Diabetic ketoacidosis is no exception, and many patients with type 1 diabetes mellitus continue to get episodes of ketoacidosis. The true incidence of diabetic ketoacidosis in patients with end-stage kidney disease has not been systemically studied. Long-term follow-up has shown that up to 70% of patients with type 1 diabetes mellitus die due to end-stage kidney disease, macrovascular disease, or diabetic ketoacidosis.[10,11]

Search strategy

We reviewed articles related to diabetic ketoacidosis and end-stage kidney disease, hemodialysis, peritoneal dialysis, or kidney transplant in PubMed. Studies conducted in human and published in the English language were included. Articles where hemodialysis or peritoneal dialysis were performed for acute kidney injury or solely to treat acidosis, electrolytes abnormalities, or acute renal failure were excluded. References from the selected articles were also reviewed and included if they did not appear in the initial search result.

In patients with kidney disease, the clinical presentation of diabetic ketoacidosis may vary significantly due to the degree of renal impairment and dialysis modality. These differences are due to their inability to regulate volume and electrolytes and handle the excessive acid load. Dialysis therapy may, by itself, alter the clinical presentation.

Understanding the pathophysiological differences in renal patients and the impact of various forms of renal replacement therapy are pivotal in the recognition and appropriate management of diabetic ketoacidosis in this group of patients.

Pathophysiological changes during diabetic ketoacidosis in patients with normal kidneys

A relative or absolute deficiency of insulin results

in hyperglycemia. High serum glucose level results in increased serum osmolality, resulting in a shift of water from the intracellular compartment to the extracellular compartment. Increased osmolality also results in increased thirst, and hence increased water intake. High glucose levels act as osmotic diuretic agents, leading to extracellular volume depletion. The overall volume effect of hyperglycemia is intracellular, interstitial, and intravascular dehydration.

Normally, insulin pushes glucose and potassium from the extracellular compartment to the intracellular compartment. Lack of insulin, therefore, results in hyperglycemia and hyperkalemia. An additional, a minor role is played by the intracellular generation of ketoacids and resultant shift of potassium from intracellular to extracellular compartment.[12] Some of this excess extracellular potassium is excreted through the urine along with the osmotic diuresis. Insulin deficiency thus results in intracellular potassium deficit with higher serum potassium levels. The net result is hyperkalemia with lower than normal total body potassium.

Intracellular energy pathway shifts from carbohydrate-based to lipid-based metabolism. The end-products of carbohydrate-based metabolism are carbon dioxide and water, which are easily excreted by the lungs and kidneys. The end-products of lipid metabolism are keto-acids. Of these ketoacids, acetone being highly volatile, is excreted by the lungs. Non-volatile ketoacids are dependent on effective kidney function for clearance. Generation of these ketoacids out-paces the excretion, and thus results in accumulation, leading to ketoacidosis.

In summary, insulin deficiency among patients with normal kidney function results in hyperglycemia, hyperkalemia with total body potassium deficit, ketoacidosis, and dehydration at the cellular, interstitial and intravascular levels.

Pathophysiological changes in ketoacidosis in patients with kidney disease

Patients with early stages of kidney disease may follow pathophysiological changes during hyperglycemia similar to normal subjects. Their capability to excrete water may be compromised with kidney function decline.[13,14] This inability to pass water leads to a different set of challenges. In anuric patients, hyperglycemia results in hyperosmolality leading to cellular dehydration. At the same time, thirst stimulation results in increased water intake.

Since osmotic diuresis is impaired, these subjects are unable to get rid of excessive water. This results in an increased interstitial and intravascular volume. A sudden shift of large volume from the cellular compartment to the intravascular compartment may lead to hypertension and pulmonary edema. Acidosis results in a shift of potassium from the cellular to the extracellular compartment. Insulin deficiency results in the inability of extracellular potassium to re-enter the cells. Unlike subjects with normal kidney function, this potassium cannot be readily excreted in subjects with impaired kidney function. The whole sequence leads to the development of hyperkalemia without a change in total body potassium. The inability of the kidneys to excrete fixed ketoacids results in the rapid development of acidosis.[15] In summary, diabetic ketoacidosis in a subject with renal failure results in hyperglycemia, hyperkalemia with unchanged total body potassium, severe ketoacidosis, intravascular dehydration with expanded interstitial and intravascular volume.

Pathophysiological changes in ketoacidosis in subjects with kidney failure and on renal replacement therapy

HEMODIALYSIS DEPENDENT SUBJECTS

Most dialysis solutions contain a low concentration of glucose to prevent hypoglycemia during hemodialysis treatment. In general, the glucose concentration in the dialysate is lower than the plasma, and overall a dialysis session results in a net negative glucose balance. An individual with pre-dialysis hyperglycemia may have improved serum glucose when tested immediately post-dialysis.[16] Removal of glucose during a dialysis session may be significant enough to require a different dose of basal insulin on dialysis and non-dialysis days.[17] Dialysis therapy also corrects hyperkalemia and acidosis associated with hyperglycemia. The cellular metabolic effects of insulin deficiency are not corrected by dialysis. Ketogenesis may continue unabated, during or after dialysis, in the absence of insulin. The clinical presentation of these subjects may vary depending upon the timing of their presentation in relation to their last dialysis session, fluid removed during the session, oral intake of fluid since the last session, and other factors altering the volume, such as, vomiting or diarrhea. Furthermore, acidosis and hyperkalemia may be partially corrected or even normalized

immediately after a dialysis session despite on-going ketogenesis. In the immediate post-dialysis period, diabetic ketoacidosis may be missed due to lower glucose levels and correction of acidosis and hyperkalemia due to dialysis therapy. Acidosis and hyperkalemia may redevelop with time and will be most severe if the patient presents before the next dialysis session is due.

PERITONEAL DIALYSIS

Peritoneal dialysis fluids generally contain high glucose concentration and, unlike hemodialysis, results in a positive glucose balance.[18] High serum glucose results in a lower gradient between peritoneal and serum glucose, leading to reduced ultrafiltration. These subjects may present with ultrafiltration failure and volume overload if serum glucose is poorly controlled. Hyperglycemia, in association with lower urine output, leads to a fluid shift from the cellular compartment to the extracellular compartment leading to cellular dehydration. Subjects with preserved kidney function develop osmotic diuresis resulting in extracellular and cellular dehydration. In contrast, patients with very low glomerular filtration rate and limited urine output develop extracellular hypervolemia with cellular dehydration during hyperglycemia. In such subjects, the overall volume may still be higher than baseline if the thirst mechanism is intact. These changes may manifest clinically as excessive thirst, weight gain, edema, hypertension, and pulmonary edema. Intracellular dehydration is asymptomatic if it develops slowly; otherwise, it may result in seizure and coma.[19]

SUBJECTS WITH KIDNEY TRANSPLANT

Diabetes mellitus is a common comorbidity in patients who undergo kidney transplant surgery. Non-diabetic subjects are known to be at risk of developing new-onset diabetes mellitus after transplantation (NODAT). The risk of NODAT has been reported to be as high as 32% after a solid organ transplant.[20] The risk factors for the development of NODAT include immunosuppressive agents (glucocorticoids, calcineurin inhibitors, and mTOR inhibitors), infections (hepatitis C virus and cytomegalovirus), human leukocyte antigen (HLA) matching, perioperative hyperglycemia, and hypomagnesemia.[21–24] Acute complications of diabetes mellitus are also common after kidney transplant. Approximately 19% of kidney transplanted subjects develop NODAT within three years. Diabetic ketoacidosis develops in approximately 8% of patients with NODAT.[25] The risk factors for diabetic ketoacidosis after kidney transplant include recent transplant surgery, exposure to high dose steroids, tacrolimus-based immunosuppression, lower recipient body mass index, female gender, African-American ethnicity, deceased donor kidney transplant, and younger age of recipient.[26]

After an episode of diabetic ketoacidosis at least some of these subjects may return to oral antidiabetic medications after conversion from tacrolimus to cyclosporin, under close monitoring.[27]

Kidney transplant subjects with normal functioning graft and normal urine output would have similar fluid, electrolytes, and acid-base changes as in a healthy subject. Subjects with impaired graft function may present differently in terms of fluid volume, electrolytes, and acid-base status with varying grades of renal impairment.

Management of diabetic ketoacidosis in subjects with end-stage kidney disease

Recognition of ketoacidosis may be delayed in subjects with renal failure as nausea and vomiting may be attributed to 'uremia'. Shortness of breath may be entirely attributed to volume overload, overlooking Kussmaul breathing due to acidosis. High anion-gap acidosis and hyperkalemia may be attributed to renal failure. High anion gap metabolic acidosis may be due to ketoacidosis or lactic acidosis, or a combination of these processes. The use of sodium-glucose transport protein 2 inhibitors has been associated with euglycemic ketoacidosis. Metformin-triggered inhibition of gluconeogenesis may lead to 'starvation ketosis'. For these reasons, some suggest routine measurement of serum lactic acid and ketoacids in all patients presenting with high anion gap metabolic acidosis.[28] Lower serum bicarbonate than baseline in a patient with end-stage kidney disease and diabetes mellitus should prompt a search for alternative acidosis etiology rather than assuming it to be due to chronic renal failure. Even if not frankly volume overloaded, these subjects may not tolerate aggressive hydration due to their low urine output. History of missed insulin doses or features of infection should hint toward the diagnosis of diabetic ketoacidosis. Information about the last dialysis session, pre-dialysis, and post-dialysis weight

are valuable in estimating volume status. A subject who presents above his or her pre-dialysis weight would likely be volume overloaded and benefit from a session of dialysis, especially if life-threatening hyperkalemia co-exists. Insulin is mandatory to stop and correct ketogenesis. Subjects may not require intravenous fluids unless they develop hypotension. Dialysis may help correct hyperkalemia, volume overload, and acidosis. On occasion, it may be clinically difficult to determine volume status accurately when there is a question of chest infection precipitating diabetic ketoacidosis. Fluid therapy in such subjects may be guided by central pressure monitoring. Serum electrolytes should be monitored closely, and potassium supplementation should be restricted to patients with hypokalemia.

Subject who present with a weight at or below their post-dialysis weight may be dehydrated and require fluids. Intravenous fluids, when administered, should be administered in small boluses, and pre-dialysis weight should be targeted. If the subject reaches pre-dialysis weight and yet remains hypotensive, then further fluid administration may be guided by central venous pressure monitoring and an alternative diagnosis, such as sepsis or cardiovascular disease, should be suspected.

Subjects may present with shortness of breath and volume overload while at or below their pre-dialysis weight. This may result from a massive shift of fluid from the intracellular compartment to the vascular compartment due to hyperglycemia and increased osmolality of the extracellular compartment. In such subjects, fluid shift back into the cells with insulin therapy alone may suffice. Treating these subjects with simultaneous ultrafiltration and insulin infusion may risk rapid intravascular volume depletion and hypotension during dialysis.

In subjects with kidney disease, the half-life of insulin is prolonged, and insulin dose reduction by 50% is recommended in patients with end-stage kidney disease. Despite all precautions, subjects with kidney failure and diabetic ketoacidosis remain at higher risk of complications.[29–31]

CONCLUSION

A comprehensive review should be carried out after the acute episode of ketoacidosis is managed to prevent further events. Compliance with diet and insulin administration should be evaluated. The type, dose, storage, and expiry of the insulin should be evaluated. In non-compliant subjects, bio-psycho-social evaluation should be carried out to identify strategies for improved cooperation and compliance.

Reduction of steroid dose, tapering tacrolimus, or substituting it with cyclosporin, everolimus, or belatacept, may be considered in post-kidney transplant subjects. However, adjustment of such immunosuppressive therapy aimed at improving glucose tolerance must be weighed against the risk of kidney allograft rejection.[32,33]

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