REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES
Julie R. Ingelfinger, M.D., *Editor*

Electrolyte and Acid–Base Disturbances in Patients with Diabetes Mellitus

Biff F. Palmer, M.D., and Deborah J. Clegg, Ph.D.

From the Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (B.F.P.); and the Biomedical Research Department, Diabetes and Obesity Research Division, Cedars–Sinai Medical Center, Beverly Hills, CA (D.J.C.). Address reprint requests to Dr. Palmer at the Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, or at biff.palmer@utsouthwestern.edu.

N Engl J Med 2015;373:548-59.
DOI: 10.1056/NEJMra1503102

The prevalence of diabetes is increasing rapidly, and type 2 diabetes now accounts for 20 to 50% of cases of new-onset diabetes in young people.[1] Electrolyte disturbances are common in patients with diabetes and may be the result of an altered distribution of electrolytes related to hyperglycemia-induced osmotic fluid shifts or of total-body deficits brought about by osmotic diuresis. Complications from end-organ injury and the therapies used in the management of diabetes may also contribute to electrolyte disturbances. In this review, we highlight the ways in which specific electrolytes may be influenced by dysregulation in glucose homeostasis.

SODIUM

Increases in plasma glucose concentration can lead to changes in plasma sodium concentration through several mechanisms. Elevations in glucose concentration increase plasma tonicity, creating an osmotic driving force that favors the movement of water from the intracellular space to the extracellular space, thereby diluting the extracellular concentration of sodium. The plasma sodium concentration is usually low as a result of this osmotic flux of water. Increased or normal plasma sodium concentrations in the presence of hyperglycemia indicate a clinically significant deficit in total body water. A consensus statement and clinical practice guidelines on the management of hyperglycemic crises in adults recommend the addition of a correction factor of 1.6 mg per deciliter to the measured plasma sodium concentration for each 100 mg per deciliter (5.6 mmol per liter) of glucose above 100 mg per deciliter to account for the dilutional effect of glucose.[2,3] Correcting the plasma sodium concentration in patients with glycemia helps to assess the magnitude of the deficit of sodium and water and provides a reasonable initial estimate of the required tonicity of replacement fluids during the course of therapy. Correction factors predicting plasma sodium concentration after the normalization of hyperglycemia vary from a low of 1.35 mmol per liter to as high as 4.0 mmol per liter[4,5] (for additional discussion, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Such variability in the range of correction factors appears to be due to the fact that patients with preserved renal function represent an open hyperglycemic system that introduces a number of variables, all difficult to quantify, and renders the use of a standardized correction factor imprecise. It should be emphasized that the corrected sodium concentration at the time of sampling does not account for the effects of osmotic diuresis and fluid intake during treatment, both of which are highly variable and unpredictable. Frequent calculations of the corrected sodium concentration, along with

close monitoring of urinary losses, are required during the management of all hyperglycemic crises.

The stabilization of hemodynamics with normal saline is the initial goal of fluid therapy in patients with a hyperglycemic crisis. During the course of care, a switch to more hypotonic fluids may be required for patients in whom a deficit in total body water has been determined. Isotonic saline infusion should be continued when the corrected plasma sodium concentration is reduced.[2,3,6] As Kamel and Halperin recently stated, the fluids selected for administration should minimize the drop in effective osmolality, particularly during the first 15 hours of therapy, in order to reduce the risk of cerebral edema.[7] Because children with diabetic ketoacidosis are at particular risk for cerebral edema, some degree of hypernatremia is acceptable during the course of treatment to minimize this complication. Use of the correction factor in patient care can be demonstrated in the case of a 29-year-old man with diabetic ketoacidosis who presents with a plasma glucose concentration of 1040 mg per deciliter (57.7 mmol per liter) and the following concentrations of electrolytes: sodium 135 mmol per liter, potassium 5.4 mmol per liter, chloride 97 mmol per liter, and bicarbonate 10 mmol per liter. When a correction factor of 1.6 is used, the corrected plasma sodium concentration is estimated to be approximately 150 mmol per liter (for a further discussion of the use of fluid therapy when treating a patient with diabetic ketoacidosis, see the Supplementary Appendix).

Certain medications that are prescribed for the management of diabetes mellitus are also associated with hyponatremia.[8] Tricyclic antidepressants, which are used to treat diabetic neuropathy, are known to stimulate the release of vasopressin. Oral hypoglycemic agents, such as chlorpropamide and tolbutamide, can cause hyponatremia, possibly by augmenting the effect of endogenous vasopressin at the level of the renal collecting duct. Insulin stimulates the arginine–vasopressin–dependent expression of aquaporin-2 in the renal collecting duct, possibly augmenting the hydro-osmotic effect of vasopressin when circulating levels are increased in response to other influences.[9] The latter effect may explain the reported association between insulin use and hospital-acquired hyponatremia in patients with diabetes.[10] Hyponatremia can also develop if a patient with uncontrolled diabetes has marked hypertriglyceridemia, even when the sodium concentration in plasma water is normal — a phenomenon called pseudohyponatremia[11] (see the Supplementary Appendix for additional discussion).

POTASSIUM

Insulin deficiency, which is more common in type 1 diabetes than in type 2 diabetes, is an important factor in the net efflux of potassium from the cell. In patients with type 2 diabetes, the insulin-mediated uptake of glucose is impaired, but the cellular uptake of potassium remains normal, a situation that is consistent with the divergence of intracellular pathways that follows activation of the insulin receptor.[12] Hyperkalemia can be caused by an increase in plasma tonicity that results from the redistribution of potassium from the intracellular space to the extracellular space.[13] The efflux of potassium from the cell is due to intracellular dehydration, which results from the osmotically induced, transcellular movement of water. This movement creates a favorable gradient for the efflux of potassium.[14] The administration of dextrose in water as a short-term therapy for hyperkalemia without the concomitant administration of insulin may worsen hyperkalemia in patients with diabetes, since the endogenous secretion of insulin in these patients may be insufficient or unpredictable and may thereby result in increases in plasma tonicity. Consider a 35-year-old woman with diabetic ketoacidosis whose laboratory values are as follows: sodium 143 mmol per liter, potassium 5.8 mmol per liter, chloride 97 mmol per liter, bicarbonate 12 mmol per liter, creatinine 1.4 mg per deciliter (123.8 μmol per liter), blood urea nitrogen 28 mg per deciliter (10 mmol per liter), and glucose 680 mg per deciliter (37.8 mmol per liter). On examination, orthostatic hypotension is noted. Initial treatment should consist of 0.9% normal saline to stabilize hemodynamic status but with no added potassium chloride, since the plasma potassium concentration is elevated (see the Supplementary Appendix for a discussion of potassium management in this patient).

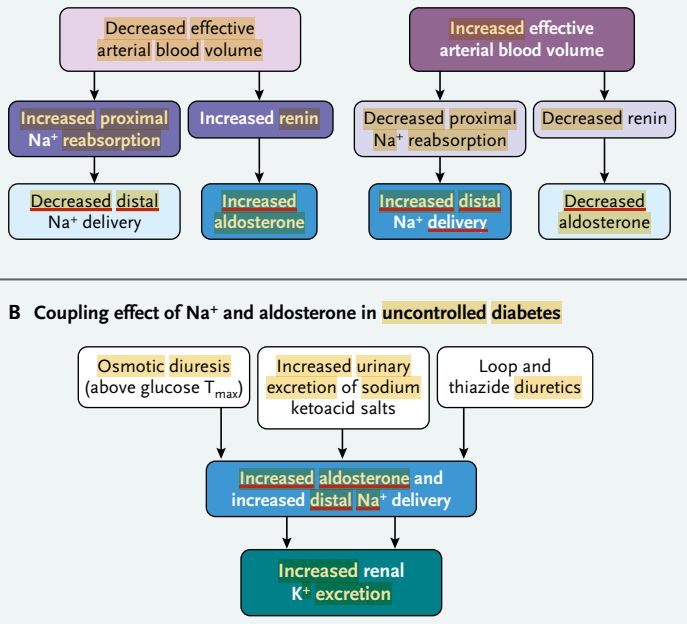

Figure 1. Volume Regulation in Persons with and without Diabetes.

In the regulation of effective arterial blood volume (Panel A), there is a balanced, reciprocal relationship between the delivery of sodium to the distal nephron and the circulating level of aldosterone that serves to maintain potassium balance. In patients with uncontrolled diabetes (Panel B), the osmotic diuretic effect of glucose (glucose T_{max} denotes the maximum rate of the reabsorption of glucose in the proximal tubule) and the excretion of sodium ketoacid salts cause an increase in the delivery of sodium to the distal nephron. At the same time, mineralocorticoid activity is increased in response to volume depletion. The coupling of the increased delivery of sodium with the increased mineralocorticoid activity results in renal potassium wasting and total-body depletion. The use of loop or thiazide diuretics also contributes to renal potassium wasting by means of this coupling effect. In addition, high flow rates in the distal nephron lower the luminal potassium concentration, providing a more favorable gradient for the diffusion of potassium into the luminal fluid. High flow in the distal nephron also activates potassium secretion by means of the calcium-activated potassium channel (or the maxi-K^+channel).

Hyperkalemia is frequently present on admission in patients with diabetic ketoacidosis, even though total-body potassium is reduced. This condition is caused by potassium wasting, which results from the increased delivery of sodium to the distal nephron coupled with increased mineralocorticoid activity[15,16] (Fig. 1). In these circumstances, the hyperkalemia is caused by a redistribution of potassium that results from hypertonicity and insulin deficiency — not by metabolic acidosis. Potassium shifts caused by metabolic acidosis are more pronounced in hyperchloremic, nonanion-gap acidosis (also called mineral acidosis) than in organic acidosis (increased anion-gap acidosis), which is present in diabetic ketoacidosis (Fig. S1 in the Supplementary Appendix).[17] In addition, potassium shifts that are the result of hypertonicity and insulin deficiency are counterbalanced by marked increases in sympathetic-nerve activity; this increased activity moves potassium into cells by stimulating β_2-adrenergic receptors.[18] In patients receiving nonselective beta-blockers, increased adrenergic activity may worsen hyperkalemia because unopposed stimulation of α-adrenergic receptors favors the cellular efflux of potassium.[19]

ACID–BASE DISTURBANCES

Diabetic ketoacidosis is characterized by the accumulation of acetoacetic acid and β-hydroxybutyric acid.[20] Ketoacidosis results when the rate at which hepatic ketoacid is generated exceeds peripheral utilization and the concentration of ketoacid in the blood increases. The accumulation of protons in extracellular fluid causes the decomposition of bicarbonate to carbon dioxide and water, whereas the concentration of ketoacid anions increases. Reductions in plasma concentrations of bicarbonate initially approximate increases in the anion gap (an important relationship discussed more fully by Kamel and Halperin).[7] Although anion-gap acidosis is the dominant disturbance in diabetic ketoacidosis, hyperchloremic normal-gap acidosis can also be present, depending on the stage of the disease process[21-23] (Fig. 2). Resuscitation with balanced electrolyte solutions can mitigate the severity of normal-gap acidosis during the recovery phase.[24]

The kidneys are not a site of primary involvement in diabetic ketoacidosis; in patients with normal renal function, the kidney compensates with an increase in the net excretion of acid, which is reflected primarily in high levels of urinary ammonium. When there is a loss of organic acid anions, the amount of ammonium in the urine can be estimated by measurement of the urinary osmolal gap, which is defined as the difference between measured urinary osmo-

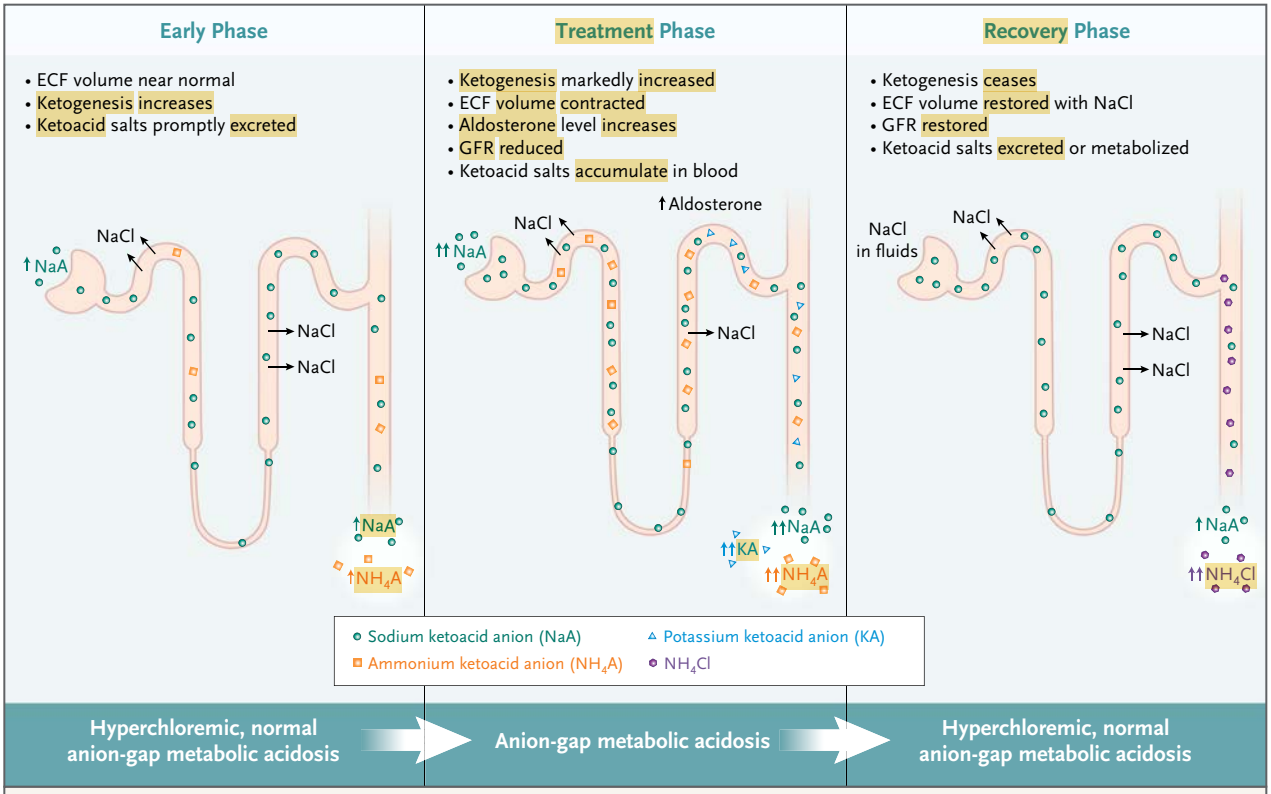

Figure 2. Phases of Metabolic Acidosis in Patients with Diabetes.

In the early phase of ketoacidosis, when the volume of extracellular fluid (ECF) is close to normal, the ketoacid anions produced will be rapidly excreted by the kidney as sodium and potassium salts. The urinary loss of ketone salts leads to the contraction of the volume of ECF and signals the renal retention of dietary sodium chloride. The proton of the ketoacid reacts with bicarbonate to generate water and carbon dioxide, which are expired through the lungs. The net effect is the development of a hyperchloremic normal-gap acidosis. This process has been referred to as an indirect loss of sodium bicarbonate.[7] As the ketogenic process becomes more accelerated and as volume depletion becomes more severe, a larger proportion of the generated ketoacid salts are retained within the body, thus increasing the anion gap. At this point, glomerular filtration rate (GFR) is typically reduced and a patient requires treatment and admission to a hospital. During the recovery phase, the anion-gap metabolic acidosis is transformed once again into a hyperchloremic, normal anion-gap acidosis. Treatment leads to the termination of ketoacid production. As the ECF volume is restored, there is increased renal excretion of the sodium salts of the ketoacid anions. The indirect loss of bicarbonate, combined with the retention of administered sodium chloride, accounts for the redevelopment of the hyperchloremic, normal-gap acidosis. In addition, the potassium and sodium administered in solutions containing sodium chloride and potassium chloride enter into cells in exchange for hydrogen ions. The net effect is the infusion of hydrogen chloride into the extracellular fluid. The normalization of the acid–base balance is accomplished over a period of several days as the bicarbonate deficit is corrected as bicarbonate is regenerated by the kidney.

lality and estimated urinary osmolality, which is derived from the following equation[25,26]:

$$\text{Urinary osmolality} = ([2 \times \text{urinary Na}^+] + [2 \times \text{urinary K}^+]) + (\text{urinary urea nitrogen in milligrams per deciliter} \div 2.8) + (\text{urinary glucose in milligrams per deciliter} \div 18).$$

In the absence of glycosuria, the glucose portion of the equation can be deleted. A large increase in the urinary osmolal gap suggests increased excretion of ammonium coupled with either chloride or ketoanions, a process that is consistent with the extrarenal nature of the acidosis and intact renal function. However, in some patients with diabetic acidosis, the gap may be lower in the absence of a defect in the renal response to the acid load. Such a response would occur in patients with a low glomerular filtration rate (GFR) when the filtered load of sodium is reduced. The resultant decrease in the rate of ATP expenditure required for sodium

transport and the oxidation of ketoacid anions in cells of the proximal tubule lower the utilization of glutamine and hence diminish the rate of ammoniagenesis.[27,28] Measurement of the urinary osmolal gap is most useful in the evaluation of patients with hyperchloremic acidosis and a normal gap. (This condition typically develops during the recovery phase of diabetic ketoacidosis, after normalization of the anion gap.) The urinary osmolal gap is measured to determine whether there is an appropriate increase in the urinary excretion of ammonium, which leads to resolution of the acid–base disorder. A low urinary osmolal gap in patients with persistent hyperchloremic normal-gap acidosis suggests tubular dysfunction.

In the past, nitroprusside tablets or reagent strips were used to detect ketoacids. Despite recent advances that permit direct quantification of β-hydroxybutyrate levels, measured concentrations of ketone bodies often cannot completely account for the increased anion gap, and in many patients hyperlactatemia may be contributory.[29] Lactate levels may increase in response to hyperadrenergic activity, even in the absence of tissue hypoperfusion.[30] Another contributor to the increased gap is the accumulation of D-lactic acid caused by the increased production of methylglyoxal through the glyoxalase pathway.[31] Although factors such as acidosis, hyperosmolality, and cerebral hypoperfusion have been implicated in the altered sensorium that is often present in patients with diabetic ketoacidosis, we speculate that D-lactate may also play a role.[32]

The treatment of diabetic ketoacidosis involves the administration of insulin and intravenous fluids to correct volume depletion. Alkali therapy is generally not required because insulin administration will slow the rate of ketoacid production, and the oxidation of ketoanions will lead to the regeneration of bicarbonate,[33] but there are certain circumstances in which alkali therapy may be indicated.[7] Alkali therapy has been linked to an increased risk of cerebral edema in children.[7,33]

Metformin, which is used in the treatment of type 2 diabetes, can in rare circumstances lead to lactic acidosis, but the risk is quite low and is in fact indistinguishable from the background rate of lactic acidosis among patients with type 2 diabetes.[34] The risk increases when renal function declines abruptly; because metformin is cleared by the kidneys, metformin levels become elevated when renal function is impaired. For instance, a patient with clinically stable type 2 diabetes who is being treated with metformin and in whom gastroenteritis then develops will be subject to volume depletion. The resulting increase in efferent arteriolar tone mediated by angiotensin II will raise the intraglomerular pressure to counterbalance the decrease in renal perfusion, thereby stabilizing the GFR and preventing the accumulation of metformin. If such a patient is receiving an angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), this counterbalancing effect will be lost because of the decrease in efferent arteriolar tone that results from treatment with inhibitors of the renin–angiotensin system.[35] Metformin accumulates if there is a severe reduction in the GFR, which may lead to lactic acidosis. Nonsteroidal antiinflammatory drugs can increase the risk of metformin accumulation because they increase afferent arteriolar tone, especially in patients with decreased renal perfusion, thereby causing an abrupt and significant reduction in the GFR. Metformin is readily removed with dialysis therapy since it has a low molecular weight and does not bind proteins; however, prolonged extracorporeal therapy is generally required to lower the level of metformin, since it has a high volume of distribution and two-compartment elimination kinetics.[36,37]

HYPERKALEMIC RENAL TUBULAR ACIDOSIS

Hyperkalemic renal tubular acidosis (type 4 renal tubular acidosis) is a common condition among patients with diabetes and overt nephropathy. The disease is characterized by disturbances in nephron function, which lead to impaired renal excretion of hydrogen and potassium and result in hyperkalemia and a hyperchloremic normal-gap acidosis (Fig. 3). Type 4 renal tubular acidosis may be present even in

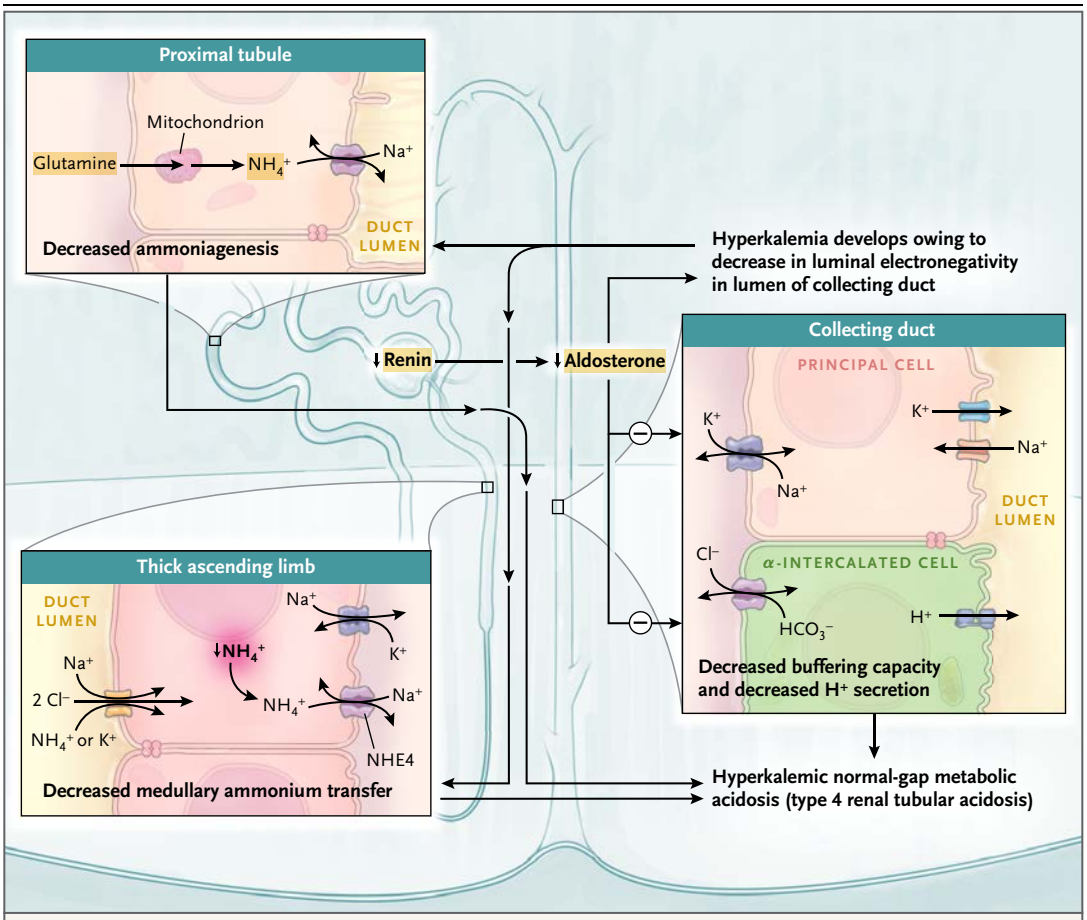

Figure 3. Pathogenesis of the Electrolyte Pattern in Type 4 Renal Tubular Acidosis.

In normal circumstances, the reabsorption of sodium in the collecting duct, driven by aldosterone, generates negative potential in the lumen, which serves as a driving force for the secretion of potassium by the principal cell and of hydrogen ions by the α-intercalated cell. Impaired sodium reabsorption in the principal cell — caused by either hyporeninemic hypoaldosteronism or impairment in the function of the collecting duct — leads to a decrease in luminal electronegativity. This decrease impairs secretion of potassium and of hydrogen ions, contributing to hyperkalemia and metabolic acidosis. The hyperkalemia further impairs acidification by decreasing the amount of ammonium available to act as a urinary buffer. First, hyperkalemia decreases the production of ammonium in the proximal tubule. The precise mechanism by which this occurs is not currently known, but it may involve the entry of potassium into cells in exchange for protons, which would raise the intracellular pH. Second, the transport of ammonium in the thick ascending limb is inhibited by the large increase in the concentration of potassium in the lumen, which effectively competes with ammonium for transport on the sodium–potassium–chloride cotransporter. Ammonium normally exits the basolateral surface of the cell through sodium–proton exchanger 4 (NHE_4). The net excretion of acid decreases as a result of the limited availability of a buffer combined with a decreased capacity for the secretion of hydrogen ions. The urinary osmolal gap is not increased, which indicates that there is little or no excretion of ammonium in the urine. Patients in whom type 4 renal tubular acidosis is caused by a defect in mineralocorticoid activity typically have a urinary pH of less than 5.5, reflecting a more severe defect in the availability of ammonium than in the secretion of hydrogen ions. In patients with structural damage, the secretion of hydrogen ions is impaired throughout the collecting duct (both cortical and medullary segments) such that the urinary pH may be more alkaline than it is in patients who have impaired mineralocorticoid activity alone.

Table 1. Electrolyte Disturbances in Diabetes Mellitus.

Disturbance	Mechanism or Cause	Comment	Treatment
Hyponatremia	Osmotically induced movement of water from intracellular to extracellular space; increased thirst and water intake; increased secretion of vasopressin, which limits renal excretion of water	Net effect of increased glucose levels in blood is movement of water from intracellular to extracellular compartments; renal loss of water caused by glycosuria determines sodium concentration	In hyperglycemic crisis, after fluid resuscitation, continue administration of 0.9% normal saline for corrected sodium concentration of <135 mmol/liter
	Medications used in treatment of diabetes		Withdraw offending medication, if clinically feasible
Hypernatremia	Hypotonic fluid loss in urine caused by osmotic diuretic effect of glycosuria	During initial treatment of hyperglycemic crisis, effective plasma osmolality should not be reduced during first 15 hr of treatment, in order to minimize risk of cerebral edema	Infuse 0.9% normal saline (with 30–40 mmol potassium chloride/liter if potassium required) to maintain effective plasma osmolality in the first 15 hr of therapy; then use 0.45% sodium chloride if corrected sodium concentration is normal or >145 mmol/liter
Hypokalemia	Cell shift in which potassium moves from extracellular to intracelluar space; may occur after administration of insulin, correction of hypertonicity, or β_2-adrenergic stimulation*	Increased renal excretion results from increased delivery of sodium to collecting duct in presence of increased mineralocorticoid activity	During treatment of hyperglycemic crisis with 3.5–5.2 mmol potassium/liter, add 20–40 mmol potassium to each liter of fluid
Hyperkalemia	Cell shift intracelluar to extracellular space-caused by insulin deficiency or hypertonicity (not metabolic acidosis)*	Cell shift causes transient hyperkalemia	In hyperglycemic crisis in which potassium concentration is >5.2 mmol/liter, do not add potassium to replacement fluids (recheck potassium concentration every 2 hr)
	Impaired renal excretion	Impaired renal excretion causes chronic hyperkalemia	In type 4 renal tubular acidosis, start low-potassium diet, discontinue offending medications if possible, maximize use of diuretics, correct acidosis if present, consider fludrocortisone in absence of fluid overload or hypertension
Anion-gap metabolic acidosis	Fully established ketoacidosis (volume depletion, often with reduced glomerular filtration rate)	Levels of L-lactate and D-lactate are increased in diabetic ketoacidosis	Initiate fluid resuscitation and insulin; bicarbonate therapy not routinely indicated, but if pH ≤6.9, infuse 100 mmol bicarbonate in 400 ml sterile water plus 20 mmol potassium chloride at rate of 200 ml/hr over 2 hr and repeat until pH ≥7.0
Hyperchloremic normal-gap metabolic acidosis	In the early phase or in the recovery phase of diabetic ketoacidosis	Hypoaldosteronism or disturbances in function of collecting duct account for impaired excretions of potassium and hydrogen in type 4 renal tubular acidosis	Monitor patient; resolution will occur during recovery phase of diabetic ketoacidosis unless renal function is impaired†
	Renal tubular acidosis of renal insufficiency, type 4 renal tubular acidosis		In type 4 renal tubular acidosis, treat hyperkalemia as indicated above
Metabolic alkalosis	Vomiting, which often occurs in patients with diabetic ketoacidosis and diabetic gastroparesis	Plasma bicarbonate concentration higher than expected given extent of increase in anion gap in ketoacidosis	Restore volume of extracellular fluid with 0.9% normal saline, correct potassium deficit if present
	Administration of loop or thiazide diuretics		Discontinue drug, if feasible, administer chloride-containing solutions intravenously if indicated

Disturbance	Mechanism or Cause	Comment	Treatment
Hypomagnesemia	Renal magnesium wasting caused by osmotic diuretic effect of glycosuria and metabolic acidosis, impaired gastrointestinal absorption, administration of proton-pump inhibitors or thiazide diuretics	Effects of hypoalbuminemia can be corrected by adjustment of serum magnesium concentration to 0.01 × (40 − measured albumin level [in g/liter]); hypomagnesemia can cause hypokalemia as result of renal potassium wasting and hypocalcemia	Provide magnesium supplement; oral supplements preferred, with intravenous magnesium indicated in symptomatic patients (e.g., those with arrhythmias or neuromuscular irritability); magnesium supplementation may reduce risk of diabetes
	Metabolic acidosis, which increases concentration of ultrafilterable magnesium		
	Gastrointestinal loss of magnesium as a result of diarrhea, which may occur in autonomic neuropathy		
Hypermagnesemia	Insulin deficiency and metabolic acidosis, leading to cell shift in which magnesium flows out of cell	Degree of elevation is mild; correction of acidosis, administration of insulin, and β_2–adrenergic stimulation can unmask total-body deficit if present	No specific therapy indicated
Hypocalcemia	Urinary loss of vitamin D–carrying protein in the nephrotic syndrome, altered set point for release of parathyroid hormone	To correct for effect of hypoalbuminemia, add 0.8 mg calcium/dl for every decrease of 1 g/dl in plasma albumin concentration	Correct deficiency in vitamin D, if present
			Correct magnesium deficit, if present
Hypercalcemia	Volume depletion, thiazide diuretics	Severity usually mild when associated with thiazide diuretics or volume depletion	Restore extracellular volume, discontinue or minimize dose of diuretic
Hypophosphatemia	Total-body depletion resulting from osmotic diuresis	In diabetic ketoacidosis, treatment with insulin and correction of acidosis unmasks phosphate deficit	Consider phosphate supplementation — not routinely indicated in diabetic ketoacidosis but is indicated for skeletal-muscle weakness, respiratory suppression, or rhabdomyolysis, with 20–30 mmol potassium phosphate/liter added to replacement fluid; maximal rate of infusion should be no greater than 4.5 mmol/hr to avoid hypocalcemia and hypomagnesemia
Hyperphosphatemia	Present in diabetic ketoacidosis, as a result of insulin deficiency and metabolic acidosis	Elevated serum concentrations of phosphate can be present despite total-body depletion in diabetic ketoacidosis	In diabetic ketoacidosis, provide insulin therapy and correct acidosis, both of which will correct hyperphosphatemia
	Advanced chronic kidney disease		In diabetic nephropathy, manage hyperphosphatemia as suggested for other causes of chronic kidney disease (e.g., low-phosphate diet, phosphate binders)

* A cell shift refers to the flow of electrolytes into or out of a cell.

† Bicarbonate therapy may be considered when a major fraction of acidemia is caused by normal anion-gap acidosis, since the amount of circulating ketoacid anions available for metabolism to bicarbonate, combined with rapid infusion of saline, can worsen acidemia.[7] Patients with diabetic nephropathy and an estimated glomerular filtration rate of <30 ml per minute may also benefit, since ketoacid oxidation will be reduced.

patients with mild-to-moderate diabetic nephropathy, and the magnitude of the hyperkalemia and acidosis can be disproportionately severe relative to the observed reductions in GFR. A deficiency in circulating levels of aldosterone or disease affecting the collecting duct may lead to type 4 renal tubular acidosis, which results in a defect in the distal secretion of hydrogen ions.[38] In such cases, multiple alterations in the renin–angiotensin system effectively reduce the circulating levels or activity of mineralocorticoids (Table S1 in the Supplementary Appendix). Hyporeninemic hypoaldosteronism and volume expansion occur in many patients with diabetes mellitus. Although these conditions are generally thought to be caused by a reduced GFR in association with the development of diabetic nephropathy, studies in animals show that the direct effects of insulin on receptors in the distal nephron decrease the activity of — lysine-deficient protein kinase 4 (WNK4), which leads to pathophysiological changes similar to those seen in the syndrome of familial hyperkalemic hypertension (pseudohypoaldosteronism type 2).[39,40]

Most patients do not require treatment for type 4 renal tubular acidosis unless they have a concurrent illness that worsens the hyperkalemia and acidosis. Consequently, the primary goal of therapy is to correct the hyperkalemia. In many instances, reducing the plasma potassium concentration will correct the acidosis. Discontinuing drugs that are known to interfere with the synthesis or activity of aldosterone is the first-line therapy.[41] In patients with aldosterone deficiency who have neither hypertension nor fluid overload, the administration of synthetic mineralocorticoids (e.g., fludrocortisone) is effective (Table S1 in the Supplementary Appendix). In most patients with hypertension, the administration of a thiazide diuretic (or, in patients with an estimated GFR of <30 ml per minute, a loop diuretic) is an alternative.[41] The administration of 30 to 40 mmol of bicarbonate per day is usually sufficient to raise the plasma bicarbonate level above 20 mmol per liter in patients with persistent metabolic acidosis. The primary complication associated with such therapy is volume overload, although sodium retention is lower with sodium bicarbonate than with sodium chloride in patients with chronic kidney disease.[42] The management of type 4 renal tubular acidosis in patients with diabetes can present a therapeutic dilemma regarding the selection of drugs that block the renin–angiotensin system. Consider a 63-year-old man with type 2 diabetes mellitus complicated by diabetic nephropathy who presents with heart failure with a reduced ejection fraction. Laboratory analyses of electrolytes show a sodium level of 141 mmol per liter, potassium 5.2 mmol per liter, chloride 107 mmol per liter, and bicarbonate 19 mmol per liter. Although an ACE inhibitor or ARB would be useful to slow the progression of renal disease and treat the underlying heart failure, these drugs may also increase the risk of life-threatening hyperkalemia (see the Supplementary Appendix for further discussion of the management of this case).

DIVALENT CATIONS AND PHOSPHORUS

Disturbances in divalent-cation and phosphorus homeostasis are related to hyperglycemia and are thus common in patients with diabetes. Epidemiologic studies suggest that low magnesium intake is associated with an increased risk of diabetes, whereas a higher magnesium intake is associated with a decreased risk of diabetes.[43] In addition, hypomagnesemia may impair glucose disposal and contribute to cardiovascular disease, retinopathy, and nephropathy.[44] The incidence of hypomagnesemia in patients with type 2 diabetes ranges widely, from 13.5% to 47.7%.[45] Causes include poor oral intake and the chronic diarrhea associated with autonomic neuropathy. Proton-pump inhibitors impair the gastrointestinal absorption of magnesium. This effect may be the result of a drug-induced decrease in the pH of the intestinal lumen that alters the affinity of transient receptor potential melastatin-6 and melastatin-7 (TRPM6 and TRPM7) channels on the apical surface of enterocytes for magnesium.[46]

In patients with diabetic ketoacidosis, the osmotic diuresis resulting from poor glycemic control may lead to renal magnesium wasting. However, serum magnesium levels may be mildly increased as a result of insulin deficiency and

metabolic acidosis, despite the depletion of total body stores. The administration of insulin and the correction of acidosis shift magnesium into cells, with the result that the bodily deficit is unmasked. In addition, increased adrenergic activity may contribute to intracellular shifts in magnesium.[47]

Hypocalcemia is a potential complication of diabetic nephropathy in patients with the nephrotic syndrome, since the nephrotic state leads to urinary loss of 25-hydroxyvitamin D_3 and its carrier protein.[48] Alterations in the set point for parathyroid hormone release and circulating levels in patients with diabetes are reminiscent of those found in hypoparathyroidism, having the potential to exacerbate the tendency for the development of hypocalcemia.[49,50] Hypomagnesemia can be a cause of hypocalcemia because magnesium deficiency can result in impaired release of and skeletal resistance to parathyroid hormone. Primary hyperparathyroidism should be considered in patients with diabetes who have hypercalcemia, since in such persons primary hyperparathyroidism occurs at a rate that is several times as high as that in the general population.[51] Hypercalcemia also occurs in patients with volume depletion, which leads to the increased reabsorption of renal calcium.[52]

Derangements in phosphate metabolism are evident in patients with diabetic ketoacidosis. Hyperphosphatemia is frequently present on admission, with reported levels as high as 17 mg per deciliter[53] owing to insulin deficiency and metabolic acidosis. Insulin treatment and correction of the acidosis causes plasma phosphate concentrations to fall sharply as a result of the shift into cells, unmasking an average total-body deficit of about 1 mmol per kilogram of body weight.[2,54] Phosphate depletion also results from the urinary losses caused by osmotic diuresis. In the absence of diabetic ketoacidosis, hyperphosphatemia can be present with acute kidney injury or advanced chronic kidney disease (as is also the case in patients without diabetes). Consider a 38-year-old woman with diabetic ketoacidosis whose laboratory values are as follows: sodium 130 mmol per liter, potassium 5.4 mmol per liter, chloride 98 mmol per liter, bicarbonate 10 mmol per liter, glucose 724 mg per deciliter, and phosphate 7.8 mg per deciliter. After 1 day of treatment, the phosphate concentration has decreased to 1.8 mg per deciliter (see the Supplementary Appendix for a discussion of phosphate management in this patient).

Randomized trials of phosphate therapy in patients with ketoacidosis have not shown that this therapy provides clinical benefit; therefore, routine administration of phosphate is not recommended.[55] In patients at risk for potential complications of hypophosphatemia, such as weakness in the heart or skeletal muscles, rhabdomyolysis, or hemolytic anemia, potassium phosphate can be added to replacement fluids. Of course, hypocalcemia and hypomagnesemia are potential complications of phosphate administration (Table 1).

SUMMARY

In summary, the dysregulation of glucose homeostasis leads to many direct and indirect effects on electrolyte and acid–base balance. Since the high prevalence of diabetes ensures that clinicians in virtually every medical specialty will interact with these patients, familiarity with related electrolyte abnormalities is important.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. Atlanta: Centers for Disease Control and Prevention, 2014.
2. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335-43.
3. Goguen J, Gilbert J. Hyperglycemic emergencies in adults. Can J Diabetes 2013;37:S72-S76.
4. Roscoe JM, Halperin ML, Rolleston FS, Goldstein MB. Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression. Can Med Assoc J 1975;112:452-3.
5. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999;106:399-403.
6. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract 2011;94:340-51.
7. Kamel KS, Halperin ML. Acid–base problems in diabetic ketoacidosis. N Engl J Med 2015;372:546-54.
8. Palmer BF, Gates JR, Lader M. Causes

and management of hyponatremia. Ann Pharmacother 2003;37:1694-702.
9. Bustamante M, Hasler U, Kotova O, et al. Insulin potentiates AVP-induced AQP2 expression in cultured renal collecting duct principal cells. Am J Physiol Renal Physiol 2005;288:F334-F344.
10. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. Novel risk factors for hospital-acquired hyponatraemia: a matched case-control study. Clin Endocrinol (Oxf) 2007; 66:367-72.
11. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. Am J Nephrol 2013;38:50-7.
12. Nguyen TQ, Maalouf NM, Sakhaee K, Moe OW. Comparison of insulin action on glucose versus potassium uptake in humans. Clin J Am Soc Nephrol 2011;6: 1533-9.
13. Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. Am J Kidney Dis 2010;56: 387-93.
14. Tzamaloukas AH, Ing TS, Elisaf MS, et al. Abnormalities of serum potassium concentration in dialysis-associated hyperglycemia and their correction with insulin: a unique clinical/physiologic exercise in internal potassium balance. Int Urol Nephrol 2010;42:1015-22.
15. Palmer BF. A physiologic-based approach to the evaluation of a patient with hypokalemia. Am J Kidney Dis 2010;56: 1184-90.
16. Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol 2015; 10:1050-60.
17. Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. J Am Soc Nephrol 2011;22: 1981-9.
18. Christensen NJ. Plasma norepinephrine and epinephrine in untreated diabetics, during fasting and after insulin administration. Diabetes 1974;23:1-8.
19. Epstein FH, Rosa RM. Adrenergic control of serum potassium. N Engl J Med 1983;309:1450-1.
20. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983; 309:159-69.
21. Elisaf MS, Tsatsoulis AA, Katopodis KP, Siamopoulos KC. Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis. Diabetes Res Clin Pract 1996;34:23-7.
22. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. Nephron 1990;54:1-6.
23. Adrogué HJ, Eknoyan G, Suki WK. Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated. Kidney Int 1984;25:591-8.
24. Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med 2011;29:670-4.
25. Halperin ML, Margolis BL, Robinson LA, Halperin RM, West ML, Bear RA. The urine osmolal gap: a clue to estimate urine ammonium in "hybrid" types of metabolic acidosis. Clin Invest Med 1988; 11:198-202.
26. Halperin ML, Kamel KS. Some observations on the clinical approach to metabolic acidosis. J Am Soc Nephrol 2010;21: 894-7.
27. Halperin ML, Vinay P, Gougoux A, Pichette C, Jungas RL. Regulation of the maximum rate of renal ammoniagenesis in the acidotic dog. Am J Physiol 1985; 248:F607-F615.
28. Halperin ML, Cheema-Dhadli S. Renal and hepatic aspects of ketoacidosis: a quantitative analysis based on energy turnover. Diabetes Metab Rev 1989;5:321-36.
29. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care 2012;27: 132-7.
30. Bolli G, Cartechini MG, Compagnucci P, et al. Adrenergic activity and glycometabolic compensation in patients with diabetes mellitus. Minerva Med 1979;70: 3783-95.
31. Lu J, Zello GA, Randell E, Adeli K, Krahn J, Meng QH. Closing the anion gap: contribution of D-lactate to diabetic ketoacidosis. Clin Chim Acta 2011;412:286-91.
32. Nyenwe EA, Razavi LN, Kitabchi AE, Khan AN, Wan JY. Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis. Diabetes Care 2010;33: 1837-9.
33. Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis — a systematic review. Ann Intensive Care 2011;1:23.
34. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA 2014; 312:2668-75.
35. Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med 2002;347:1256-61.
36. Lalau JD, Andrejak M, Morinière P, et al. Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. Int J Clin Pharmacol Ther Toxicol 1989;27: 285-8.
37. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 2009;37:2191-6.
38. Karet FE. Mechanisms in hyperkalemic renal tubular acidosis. J Am Soc Nephrol 2009;20:251-4.
39. Song J, Hu X, Riazi S, Tiwari S, Wade JB, Ecelbarger CA. Regulation of blood pressure, the epithelial sodium channel (ENaC), and other key renal sodium transporters by chronic insulin infusion in rats. Am J Physiol Renal Physiol 2006; 290:F1055-F1064.
40. Hoorn EJ, Nelson JH, McCormick JA, Ellison DH. The WNK kinase network regulating sodium, potassium, and blood pressure. J Am Soc Nephrol 2011;22:605-14.
41. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin–angiotensin–aldosterone system. N Engl J Med 2004;351:585-92.
42. Husted FC, Nolph KD, Maher JF. NaHCO3 and NaC1 tolerance in chronic renal failure. J Clin Invest 1975;56:414-9.
43. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. Diabetes Care 2004; 27:59-65.
44. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch Biochem Biophys 2007;458: 40-7.
45. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Nephrol 2007;2:366-73.
46. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. Kidney Int 2013; 83:553-6.
47. Romani AM. Cellular magnesium homeostasis. Arch Biochem Biophys 2011; 512:1-23.
48. Goldstein DA, Haldimann B, Sherman D, Norman AW, Massry SG. Vitamin D metabolites and calcium metabolism in patients with nephrotic syndrome and normal renal function. J Clin Endocrinol Metab 1981;52:116-21.
49. McNair P, Christensen MS, Madsbad S, Christiansen C, Transbøl I. Hypoparathyroidism in diabetes mellitus. Acta Endocrinol (Copenh) 1981;96:81-6.
50. Schwarz P, Sørensen HA, Momsen G, Friis T, Transbøl I, McNair P. Hypocalcemia and parathyroid hormone responsiveness in diabetes mellitus: a tri-sodium-citrate clamp study. Acta Endocrinol (Copenh) 1992;126:260-3.
51. Taylor WH, Khaleeli AA. Coincident diabetes mellitus and primary hyperparathyroidism. Diabetes Metab Res Rev 2001; 17:175-80.
52. Palmer BF. Metabolic complications associated with use of diuretics. Semin Nephrol 2011;31:542-52.
53. Franks M, Berris RF, et al. Metabolic

studies in diabetic acidosis; the effect of the administration of sodium phosphate. Arch Intern Med (Chic) 1948;81:42-55.
54. Kebler R, McDonald FD, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. Am J Med 1985;79:571-6.
55. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983;57:177-80.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Palmer BF, Clegg DJ. Electrolyte and acid–base disturbances in patients with diabetes mellitus. N Engl J Med 2015;373:548-59. DOI: 10.1056/NEJMra1503102

Supplementary Appendix: Table of contents

Page 2-3. Derivation of and variables affecting the correction factor for predicting plasma Na^+ concentration following correction of plasma glucose

Page 4-6. Case example commenting on variables affecting plasma Na^+ concentration

Page 7. Pseudohyponatremia

Page 8. Case example focusing on treatment of K^+ disorders in a patient with DKA

Page 9-10. Figure S1. Differential effect of mineral versus organic acidosis on trancellular K^+ shift

Page 11-12. Table S1. Defects in the renin-aldosterone axis in patients with type IV renal tubular acidosis

Page 13-14. Management of a patient with type IV renal tubular acidosis

Page 15. Management of a patient with hyperphosphatemia

Page 16-18. References

Derivation of and variables affecting the correction factor for predicting plasma Na^+ concentration following correction of plasma glucose

To predict the plasma Na^+ following normalization of the plasma glucose in hyperglycemic states, clinicians have historically used a correction factor a 2.8 millimole per liter drop in plasma Na^+ concentration for each 100 mg per deciliter rise in glucose, based on the assumption that 100 mg per deciliter glucose (5.6 millimole per liter) would exert the same osmotic effect as 2.8 millimole per liter of Na^+ (5.6 mmol/L NaCl). Katz argued that this assumption was incorrect, since addition of solute to extracellular fluid must result in increased osmolality at equilibrium, causing water movement to cease before normal osmolality is obtained (1). He derived a correction factor of 1.6, assuming no change in body water or solutes occur other than glucose, characteristics of a closed system. Studies in anuric patients on dialysis with hyperglycemia only treated with insulin validated this latter correction factor (2). However, other studies have reported correction factors as low as 1.35 to as high as 4 (3,4).

A number of variables have been identified which are all difficult to quantitate making a standardized correction factor inherently imprecise. For example, some factors fail to account for an estimated 4-5 liters of intracellular water in tissues such as the brain, where glucose uptake is not insulin dependent (3). Additionally, extreme or protracted hyperglycemia in the setting of preserved baseline renal function can lead to significant hypotonic urine loss causing the plasma Na^+ to increase thus lowering the correction factor. Furthermore, hypertonicity and hypovolemia stimulate intense thirst and consumption of large volumes of water. Increased water intake along with vasopressin-mediated impaired renal water excretion decreases the plasma Na^+ concentration beyond the osmotic effect mediated by glucose, therefore elevating the correction factor. Lastly, a variable further influencing the correction factor is the effect of volume status

on transfer of fluid from intracellular into the extracellular space, with less transfer occurring in edematous states and more transfer in volume depleted patients (5,6).

Case example commenting on variables affecting plasma Na^+ concentration

Successful fluid and electrolyte therapy in patients with diabetic ketoacidosis (DKA) is guided by clinical examination with particular attention to assessment of volume status, measurement of fluid input and output, and laboratory values. The following case is provided to illustrate some of the variables that can affect the plasma Na^+ concentration during the management of these patients.

Consider an orthostatic patient with a plasma Na^+ of 135 mEq/L and a plasma glucose concentration of 1040 mg/dl. The corrected plasma Na^+ is 150 mEq/L suggesting that during the course of therapy a water deficit will need to be replaced.

$$\text{Corrected } Na^+ = \text{Current } Na^+ + 0.016 \text{ (glucose -100)}$$

Importantly, the effective osmolality in plasma should not be permitted to decrease during the first 15 hours of treatment so as to reduce the risk of cerebral edema.

$$\text{Effective osmolality} = 2 \text{ x (plasma } Na^+) + \text{(plasma glucose)}/18$$

The initial goal of fluid management is stabilization of hemodynamics with normal saline. In addition to the physical exam, changes in hematocrit may be useful in making a quantitative assessment of extracellular fluid volume (7). The plasma glucose concentration will begin to fall initially by dilution and subsequently due to glucose loss in the urine. The glucose lowering effect of insulin becomes manifest later, once the concentration of fatty acids and ketoacids has decreased. In order to maintain the effective osmolality during the initial course of

therapy, the tonicity of intravenous fluids should equal the plasma osmolality if the patient is oliguric and approximate the urine osmolality during polyuria (8). In the setting of a glucose induced osmotic diuresis, the effective plasma osmolality and urine osmolality are generally similar. In this setting, administration of isotonic saline with 20-40 mmol/l of KCl would be an appropriate solution to maintain effective osmolality. Of note, K^+ should only be added to intravenous fluid once a diuresis has been established, generally after the first liter of normal saline.

The plasma Na^+ concentration should begin to increase as the plasma glucose concentration falls. One variable that can alter the expected decline in glucose with treatment is delayed gastric emptying (9). Patients with DKA consume large quantities of fluids containing glucose or water. These fluids can be retained in the stomach due to the effect of hyperglycemia to slow gastric motility. Following the institution of therapy, a failure of plasma glucose to fall coupled to further increases in the plasma Na^+ concentration despite a high rate of glucose excretion in the urine may indicate recent gastric emptying and newly absorbed glucose. Delayed gastric emptying can also be responsible for a large decrease in plasma glucose if the patient had consumed large quantities of water without sugar. This latter effect can cause the effective plasma osmolality to fall more rapidly than desired increasing the risk of cerebral edema.

Following the first 15 hours of therapy, the goal is to gradually reduce the effective osmolality to normal. In order to prevent an overly rapid fall in plasma glucose concentration and hypoglycemia, glucose is typically added to fluid therapy once the plasma glucose approaches 200 mg/dl (10). In this setting glucose should be administered in a solution that has the smallest volume of electrolyte free water such as isotonic saline or 0.45% saline so as to

avoid a rapid fall in the plasma Na^+ concentration due to desalination of body fluids. This can occur when the urine contains little glucose and the urine concentration of Na^+ and K^+ exceed the sum of plasma Na^+ and K^+ in the setting of increased vasopressin levels.

Pseudohyponatremia

Pseudohyponatremia is a phenomenon to consider when hyponatremia is present even though the Na^+ concentration in plasma water is normal. This situation occurs when chemical analysis uses indirect potentiometry. The plasma sample is first diluted before the actual measurement is obtained with this technique. The plasma Na^+ concentration is then determined by correcting for the dilution degree, making the assumption that plasma water equals 93% of the total sample volume. Since high triglycerides decrease the fraction of the plasma sample that is aqueous, the plasma Na^+ level determined will be artifactally low. When measurements are made without a dilution step (direct potentiometry), a technique available on blood gas analyzer equipment, pseudohyponatremia does not occur.

Case example focusing on treatment of K^+ disorders in a patient with DKA

Rapid shifts in K^+ during treatment of hyperglycemic crises can potentially trigger life-threatening arrhythmias. The initial K^+ level is commonly normal or high despite total body deficits ranging from 3-5 mEq/Kg in DKA and 4-6 mEq/Kg in hyperosmolar hyperglycemic states (11). The plasma K^+ should be checked every 2 hours until stabilized within the normal range of 4-5 mEq/L. Repletion is guided by the initial value and presence of adequate urine output (Table 1 in original text).

Imagine a 35 year old woman with DKA who presents with the following laboratory values (mEq/L): Na^+ 143 K^+ 5.8, Cl^- 97, HCO_3 12, creatinine 1.4 mg/dl, blood urea nitrogen 28 mg/dl, glucoses 680 mg/dl. On examination orthostatic hypotension is noted. Initial treatment should consist of 0.9% NS to stabilize hemodynamics but with no added KCl since the plasma K^+ concentration is elevated. Assume the repeat plasma K^+ level two and four hours later was 5.3 mEq/L and 4.6 mEq/L respectively. At this time, assuming urine output was at least 50 ml/hour, it would be appropriate to add 20-40 mmol KCl to each liter of 0.9% NS to prevent development of hypokalemia. As mentioned in the text, the osmolality of this solution is sufficient to prevent a fall in effective plasma osmolality which is critically important in the early stages of therapy. In patients with reduced renal function or decreased plasma aldosterone levels or activity, the total amount of K^+ needed to maintain normokalemia may be much less than expected. In the unusual patient who is hypokalemic upon presentation, K^+ supplementation should begin with fluid therapy (20-30 mmol/hr) and administration of insulin should be delayed until the plasma K^+ concentration is restored to >3.3 mEq/L so as to avoid cardiac toxicity (10).

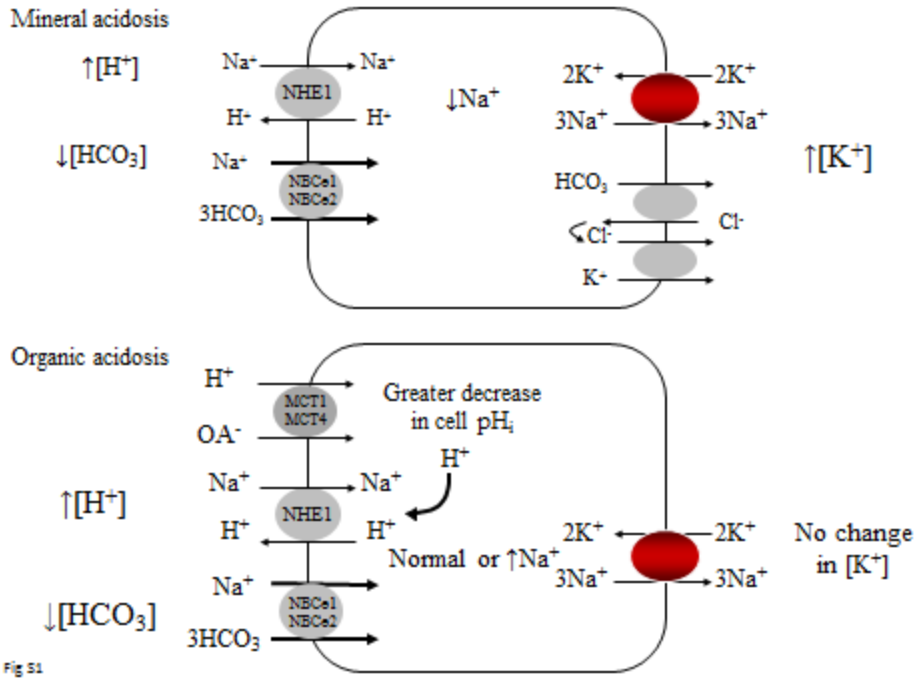

Figure S1. The effect of organic versus mineral acidosis on transcellular K^+ distribution in skeletal muscle. The effect of acidemia to cause K^+ loss from cells is due to effects of acidosis on transporters which normally regulate cell pH in skeletal muscle. In metabolic acidosis due to inorganic anions (mineral acidosis) the decrease in extracellular pH will decrease the rate of Na^+-H^+ exchange (NHE1) and inhibit the inward rate of Na^+-HCO_3 cotransport (NBCe1 and 2). The resultant fall in intracellular Na^+ will reduce Na^+-K^+ ATPase activity causing a net loss of cellular K^+. In addition, the fall in extracellular HCO_3^- concentration will increase inward movement of Cl^- by Cl^--HCO_3^- exchange further enhancing K^+ efflux by K^+-Cl^- cotransport. Loss of K^+ from the cell is much smaller in magnitude in diabetic ketoacidosis since this is an organic acidosis. In this setting there is a strong inward flux of the organic anion and H^+ via the monocarboxylate transporter (MCT1 and 4). Accumulation of the acid results in a larger fall in intracellular pH thereby stimulating inward Na^+ movement by way of Na^+-H^+ exchange and Na-

HCO_3 cotransport. Accumulation of intracellular Na^+ maintains Na^+-K^+ ATPase activity thereby minimizing any change in extracellular K^+ concentration (adapted from references 12 and 13).

Table S1. Defects in the renin-aldosterone axis in patients with type IV renal tubular acidosis

A. Causes of impaired renin release from juxtaglomerular cells

1. Chronic volume expansion leading to suppression and atrophy of the renin secreting juxtaglomerular apparatus.
2. Increased atrial natriuretic peptide release resulting from volume expansion leading to suppression of renin release (14)
3. Defect in the conversion of the precursor prorenin to active renin (15).
4. Autonomic neuropathy
5. Prostaglandin deficiency
6. Arteriosclerosis of the juxtaglomerular apparatus

B. Causes of impaired adrenal aldosterone release

1. Increased atrial natriuretic peptide release resulting from volume expansion leading to suppression of hyperkalemia-induced secretion of aldosterone
2. Intracellular K^+ depletion resulting in enzymatic defects in aldosterone biosynthesis (16)
3. Drugs such as nonsteroidal antiinflammatory agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and heparin (17)
4. Atrophy of zona glomerulosa cells secondary to chronic hyporeninemia

Multiple defects can occur in the renin-angiotensin-aldosterone system in patients with diabetes. As a result, the development of hyperkalemia due to a deficiency in circulating aldosterone represents a spectrum of disorders. Most patients demonstrate impaired renin release and are

hypertensive and respond best to diuretic therapy. A minority of patients exhibit normal renin release but have a diminished capacity to release aldosterone. These patients may exhibit less hypertension and better respond to exogenous mineralocorticoids. In addition to a reduction in circulating aldosterone, patients with diabetes may also exhibit impaired function of the collecting duct. This can be a feature of structural damage to the kidney as in interstitial renal disease or result from use of certain drugs such as spironolactone, amiloride, triamterene, and trimethoprim/sulfamethoxazole.

Management of a patient with type IV renal tubular acidosis

Consider a 63 year old man with type II diabetes mellitus complicated by diabetic nephropathy and a baseline serum creatinine concentration of 1.8 mg/dl (estimated glomerular filtration rate of 31 ml/min) who now presents with heart failure with reduced ejection fraction. Physical examination shows a blood pressure of 144/92 mmHg, basilar crackles, and trace peripheral edema. Serum electrolytes show the following (mEq/L): Na^+ 141, K^+ 5.2, Cl^- 107, HCO_3 19. The serum creatinine concentration is 2.1 mg/dl. This patient has a type 4 renal tubular acidosis likely due to hyporeninemic hypoaldosteronism and abnormal function of the collecting duct. Depending on the severity of the heart failure, decreased distal Na^+ delivery may also be reduced further contributing to impaired renal K^+ secretion. The patient poses a therapeutic dilemma since initiation of therapy with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker would be useful to slow the progression of renal disease and treat the underlying heart failure, but at the same time, make him at risk for development of life threatening hyperkalemia. There are a number of steps that can be implemented before concluding such drugs should be avoided (17).

One should review the patient's medication profile and whenever possible discontinue drugs that can impair renal K^+ excretion. He should be specifically questioned as to the use of over-the-counter non-steroidal anti-inflammatory drugs as well as herbal remedies since herbs may be a hidden source of dietary K^+. He should be placed on a low K^+ diet with specific counseling against the use of K^+ containing salt substitutes. Foods rich in K^+ include orange juice, melons, and bananas. Given the evidence of volume overload, diuretics should be initiated with the expectation that the hyperkalemia will improve. Diuretics enhance renal K^+ excretion by increasing delivery of Na^+ and flow to the collecting duct. In this patient a loop diuretic is

preferred as once the estimated glomerular filtration rate falls below 30 ml/min, thiazide diuretics become much less effective.

If the normal gap metabolic acidosis persists on diuretic therapy, administration of sodium bicarbonate to correct the acidosis is an effective strategy to minimize increases in the plasma K^+ concentration. Ensuring the patient is first on effective diuretic therapy will lessen the likelihood of developing volume overload as a complication of sodium bicarbonate administration.

Once the plasma K falls to < 5.0 mEq/L, an ACE-inhibitor or an angiotensin receptor blocker can be initiated at low dose. The K^+ should be checked within one week of starting the drug and if the K^+ is normal then the dose of the drug can be titrated upwards. If the K^+ concentration is greater than or equal to 5.6 mEq/L despite the above precautions, then such drugs may need to be avoided. Kayexalate (sodium polystyrene sulfonate) is used to treat hyperkalemia in the acute setting, however, chronic use is poorly tolerated and has been associated with mucosal injury in the lower and upper gastrointestinal tract. Newer K^+ binding drugs are currently being evaluated as a means to maintain a normal plasma K^+ in the setting of drugs that block the renin-angiotensin-aldosterone axis (18,19).

Management of phosphate in a patient with diabetic ketoacidosis

In hyperglycemic crises the serum phosphate concentration is often increased despite total body deficits as high as 5-7 mmol/kg (11). Consider a 38 year old woman with type 1 diabetes who presents with DKA and has the following electrolytes (mEq/L): Na^+ 130 K^+ 5.4, Cl^- 98 HCO_3 10, glucose 724 mg/dl, and phosphate 7.8 mg/dl. One day later the phosphate has decreased to 1.8 mg/dl. While levels typically fall during the course of therapy, prospective randomized studies have failed to show a benefit of phosphate replacement on clinical outcomes in patients with DKA (10,20,21). In addition, intravenous phosphate therapy can be complicated by clinically symptomatic hypocalcemia and hypomagnesemia. Careful phosphate repletion may be necessary in patients exhibiting manifestations of hypophosphatemia to include muscle weakness, rhabdomyolysis, respiratory failure, hemolytic anemia and in those with severe reductions in serum phosphate concentration (<1.0 mg/dl). In these settings, 20-30 mEq/L potassium phosphate can be added to replacement fluid. The maximal rate of phosphate infusion should be no greater than 4.5 mmol/hr, or a total of 90 mmol per day (22). Once a serum phosphate level of 2.0-2.5 mg/dl is achieved, changing to oral replacement therapy is safer. Assuming the above patient exhibited no manifestation of hypophosphatemia, oral supplementation would be preferred as parenteral replacement of phosphate should be reserved for those with severe or symptomatic hypophosphatemia.

References

1. Katz MA. Hyperglycemia-induced hyponatremia--calculation of expected serum sodium depression. New Engl J Med 1973;289: 843-4.

2. Tzamaloukas A, Ing T, Siamopoulos K, Rohrscheib M, Elisaf M, Raj D, Murata G. Body fluid abnormalities in severe hyperglycemia in patients on chronic dialysis: review of published reports. J Diab Compl 2008;22:29-37.

3. Roscoe J, Halperin M, Rolleston F, Goldstein M. Hyperglycemia-induced hyponatremia: metabolic considerations of serum sodium depression. Can Med Assoc J 1975;112:452-453.

4. Hillier T, Abbot R, Barrett E. Hyponatremia: Evaluation the correction factor for hyperglycemia. Am J Med 1999;106:399-403.

5. Tzamaloukas A, Ing T, Siamopoulos K, Rohrscheib M, Elisaf M, Raj D, Murata G. Body fluid abnormalities in severe hyperglycemia in patients on chronic dialysis: theoretical analysis. J Diab Compl 2007;21:374-80.

6. Moran S, Jamison R. The variable hyponatremic response to hyperglycemia. West J Med 1985;142:49-53.

7. Napolova O, Urback S, Davids M, Halperin M. Assessing the degree of extracellular fluid contraction in a patient with a severe degree of hypoglycemia. Nephrol Dial Trans 2003;18:2674-2677.

8. Halperin M, Maccari C, Kamel K. Strategies to diminish the danger of cerebral edema in a pediatric patient presenting with diabetic ketoacidosis. Pediatric Diabetes 2006;7:191-195.

9. Carlotti A, Bohn D, Jankiewicz N, Kamel K, Davids M, Halperin M. A hyperglycaemic hyperosmolar state in a young child: diagnostic insights from a quantitative analysis. QJM 2007;100:125-37.

10. Kitabchi AE, Umpierrez GE, Miles JM, and Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335-43.

11. Kitabchi A, Umpierrez G, Murphy M, Kreisberg R. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29:2739-48.

12. Palmer BF. Regulation of Potassium Homeostasis. Clin J Am Soc Nephrol 2015;10:1050-60.

13. Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. J Am Soc Nephro 2011; 22: 1981-89.

14. Bojestig M, Nystrom FH, Arnqvist HJ, Ludvigsson J, Karlberg BE. The renin-angiotensin-aldosterone system is suppressed in adults with Type 1 diabetes. J Renin Angio Aldo Sys 2000; 1: 353-6.

15. Bryer-Ash M, Fraze EB, Luetscher JA. Plasma renin and prorenin (inactive renin) in diabetes mellitus: effects of intravenous furosemide. J Clin Endo Metab 1988; 66: 454-8.

16. DeFronzo R. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Intl 1980;17:118-34.

17. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004; 351: 585-92.

18. Weir M, Bakris G, Bushinsky D, Mayo M, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B; OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 2015;372:211-21.

19. Packham DK1, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372:222-31.

20. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. Diabetes 1980;29:87-95.

21. Kebler R, McDonald F, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. Am J Med 1985;79:571-6.

22. Miller D, Slovis C. Hypophosphatemia in the emergency department therapeutics. Am J Emerg Med 2000;18:457-61.