REVIEW ARTICLE

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Electrolyte Disturbances in Patients with Chronic Alcohol-Use Disorder

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Electrolyte disturbances are common occurrences in patients with chronic alcohol-use disorder, and the quantity and duration of a given patient's alcohol consumption generally determine the clinical significance of these disturbances. Electrolyte abnormalities tend to be most severe in patients in whom protein-calorie malnutrition, vitamin deficiency, and intercurrent illness play contributory roles. However, electrolyte disorders can also be present in patients who eat three nutritious meals per day; this implicates alcohol as having a direct role in the underlying pathophysiological derangements. The prevalence of alcohol dependence among adults in the United States is estimated to be 14%, and approximately one quarter of admissions to community hospitals are related to alcohol. Therefore, it is of paramount importance for clinicians to be familiar with the genesis and treatment of alcohol-related electrolyte disorders.[1,2]

Patients in whom electrolyte disorders develop are most commonly admitted to the hospital for reasons such as abdominal pain or the onset of persistent nausea and vomiting that may or may not be related to alcohol use. Although metabolic acidosis and hyponatremia are often present on admission, other plasma concentrations may be normal or only minimally deranged, despite hidden deficits that are often large. After the initiation of therapy designed to treat acidosis and restore extracellular fluid volume, deficits are unmasked; these deficits may result in life-threatening complications. Telltale signs of chronic alcohol ingestion are precipitous decreases in plasma concentrations of phosphate, magnesium, potassium, and calcium in the first 24 to 36 hours after admission. The pathophysiology accounting for this temporal sequence of electrolyte disturbances is discussed below, with emphasis on the interrelationship between electrolyte disorders and approaches to therapy.

Acid–Base Disturbances

Persons with chronic alcohol-use disorder are prone to a variety of acid–base disturbances; one study showed that mixed disturbances were present in 78% of patients with this disorder.[3] Alcoholic ketoacidosis, which is present in 25% of patients who are admitted to the hospital with an alcohol-related disorder,[4,5] was diagnosed approximately twice per week over a 9-month period in one inner-city university-affiliated hospital.[3] Alcoholic ketoacidosis commonly occurs in patients who have discontinued alcohol ingestion before presentation, and such patients often present with abdominal pain and vomiting due to alcohol-induced gastritis or pancreatitis. Nutritional intake is typically poor before admission, and laboratory features indicate an anion-gap metabolic acidosis that is primarily due to accumulation of ketoacids and lactic acid, with a smaller contribution from acetic acid.[6] In patients with protracted vomiting, elevations in the anion gap are greater than the decrease in

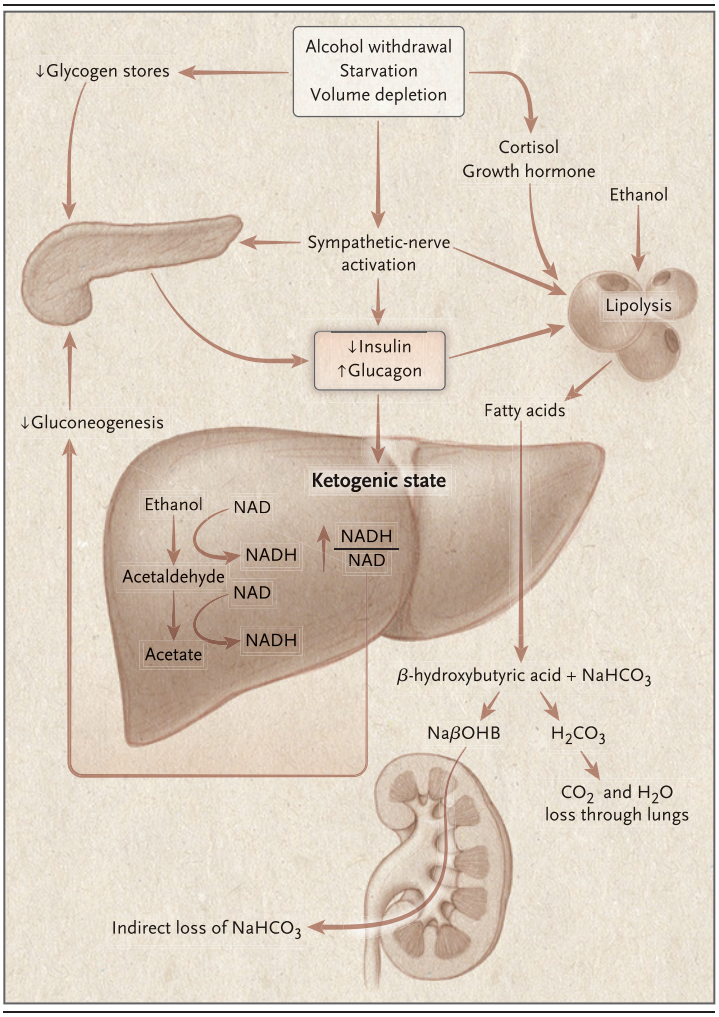

Figure 1. Mechanisms of Alcoholic Ketoacidosis.

Alcoholic ketoacidosis results when mobilization of fatty acids occurs in conjunction with a ketogenic state in the liver; this is caused by a decreased ratio of insulin to glucagon. Reduced insulin levels result from glycogen depletion from starvation, decreased gluconeogenesis, and suppression of insulin release from the pancreatic beta cells due to activation of sympathetic nerves. Activation of the sympathetic nervous system and increased levels of cortisol, growth hormone, and ethanol account for the increased magnitude of fatty acid mobilization, as compared with simple starvation.[7] Ethanol metabolism leads to an increased ratio of NADH to oxidized nicotinamide adenine dinucleotide (NAD) that contributes to decreased gluconeogenesis and facilitates production of ketone bodies, specifically β-hydroxybutyric acid. Glycogen depletion, reductions in insulin release, and increased autonomic tone provide a stimulatory effect for glucagon release. Increased glucagon levels, along with the increased ratio of NADH to NAD, enhance the ketogenic capacity of the liver. When ketoacids enter the extracellular fluid, the dissociated hydrogen reacts with bicarbonate to generate carbon dioxide and water. As a consequence, the bicarbonate concentration decreases and the salt level of the ketoacid concentration increases; this accounts for the increase in the anion gap. The excretion of the ketoacid salt into the urine with sodium or potassium (rather than hydrogen or ammonium) produces contraction of the extracellular fluid volume and stimulates renal retention of dietary sodium chloride. Volume contraction and retention of sodium chloride, combined with exogenous loss of ketoacid salts, result in the generation of a mixed anion-gap acidosis and hyperchloremic normal-gap metabolic acidosis. H_2CO_3 denotes carbonic acid, NaβOHB sodium beta-hydroxybutyrate, and $NaHCO_3$ sodium bicarbonate.

the plasma bicarbonate concentration because of the concomitant presence of metabolic alkalosis. A normal anion-gap acidosis may also be present because of indirect loss of bicarbonate in the urine (Fig. 1).[8]

Despite the presence of metabolic acidosis, only approximately 50% of patients have acidemia, and almost one third of patients have alkalemia.[3,9] Respiratory alkalosis, which is frequently the primary disorder in a mixed disturbance, is a manifestation of alcohol withdrawal, pain, severe liver disease, or underlying sepsis, all of which can have contributory roles in the disturbance.[10]

The development of ketoacidosis results from increased mobilization and delivery of long-chain fatty acids to the liver, where enzymes are activated to convert these acids to ketone bodies; this occurs under conditions of insulin deficiency and glucagon excess (Fig. 1).[11,12] Ketogenesis is also facilitated by the metabolism of alcohol to acetaldehyde and acetate, resulting in an increased ratio of reduced NADH to oxidized nicotinamide adenine dinucleotide (NAD), which leads to preferential formation of β-hydroxybutyric acid. The consequent increase in the level of β-hydroxybutyrate is important to recognize, since the use of strips or tablets that use a nitroprusside reaction, which is only sensitive to acetoacetate, to detect the presence of ketones may cause the clinician to mistakenly attribute an anion-gap acidosis to some other cause. Direct measurement of β-hydroxybutyrate levels should be performed when alcohol abuse is suspected. The increased ratio of NADH to NAD also favors conversion of pyruvate to lactate, which accounts for increased production of hepatic lactate. Peripheral tissues can oxidize lactic acid, so the degree

Box 1. A 52-year-old homeless man presents to the emergency department reporting weakness.

He typically drinks 1 pint of whisky daily. He noted the onset of epigastric pain 3 days previously but continued to drink until 1 day before presentation, when nausea and persistent vomiting developed. He reports having had no food intake over the previous 24 hours. The physical examination is noteworthy for a blood pressure of 138/90 mm Hg while the patient is supine and 110/74 mm Hg while he is standing. The pulse rate is 105 beats per minute. The remainder of the examination reveals tenderness on palpation in the epigastrium but no rebound tenderness. The laboratory values on admission are as follows: sodium, 142 mmol per liter; potassium, 3.8 mmol per liter; chloride, 92 mmol per liter; bicarbonate, 22 mmol per liter; creatinine, 1.2 mg per deciliter (106 μmol per liter); and blood urea nitrogen, 22 mg per deciliter (7.9 mmol per liter). A measurement of arterial blood gas shows a pH of 7.47 and a partial pressure of carbon dioxide of 28 mm Hg. The acid–base disturbance and the type of fluid therapy that is appropriate for correction of the underlying disorders are noted in Case 1 in the Supplementary Appendix.

of lactic acidosis tends to be mild.[6] Thus, severe lactic acidosis in a patient with alcohol abuse suggests the presence of other issues such as sepsis, tissue hypoperfusion, or thiamine deficiency.

An increased ratio of NADH to NAD leads to an inhibitory effect on hepatic gluconeogenesis that predisposes patients to hypoglycemia, which occurs in approximately one quarter of patients with alcoholic ketoacidosis.[13] Patients who present with hypoglycemia often have had reduced food intake for 14 to 24 hours after the last ingestion of alcohol. In such patients, hypoglycemia can be life threatening because the transition of alcoholic stupor to hypoglycemic coma may be imperceptible.

Initial approaches to treating ketoacidosis in a patient with chronic alcohol-use disorder should be centered on correcting any hemodynamic instability and terminating the ketogenic process. The administration of 5% dextrose in 0.9% normal saline will generally restore hemodynamic stability and begin to correct metabolic alkalosis, if present. Restoration of volume decreases sympathetic-nerve output, thereby removing an inhibitory effect on insulin release. Dextrose contained in the intravenous fluid provides a rapid additional stimulus for release of insulin. Intravenous dextrose administered at a rate of 7.0 to 7.5 g per hour usually reverses the acidosis in 12 to 24 hours.[14] Thiamine should be administered before administering glucose-containing solutions in order to decrease the risk of precipitating Wernicke's encephalopathy or Korsakoff's syndrome. Exogenous insulin should not be administered, since it can contribute to a decrease in plasma potassium, phosphorus, and magnesium levels (Box 1).

Bicarbonate therapy is not usually required, since the metabolism of lactate and ketoacid anions leads to the production of endogenous bicarbonate. In fact, exogenous bicarbonate therapy can be complicated by reductions in the ionized fraction of calcium and plasma potassium concentration. A mild normal-gap acidosis may remain after correction of the anion gap owing to indirect loss of bicarbonate in the urine. However, bicarbonate regeneration by the kidney will usually correct the bicarbonate deficit over a period of 24 to 36 hours. Many patients with chronic alcohol-use disorder will seek alternative forms of alcohol to satisfy their addiction; therefore, clinicians should be aware of the clinical features of ingestion of other toxic alcohols (Table 1).

PHOSPHORUS DISTURBANCES

Acute hypophosphatemia develops in up to 50% of patients over the first 2 to 3 days after hospitalization for problems related to chronic alcohol overuse.[15,16] Deficits in total-body stores of phosphorus are most often due to inadequate dietary intake of phosphate-rich foods such as meats, poultry, fish, nuts, beans, and dairy products. In addition, use of antacids, chronic diarrhea, vomiting, or all of these may further limit phosphorus intake.

Despite low body stores of phosphorus and hypophosphatemia, excretion of urinary phosphate is usually increased because of generalized tubular dysfunction, which is most often manifested as glycosuria, aminoaciduria, hypermagnesuria, hypercalciuria, and a decreased renal threshold for phosphate excretion.[17] The described tubular abnormalities may be related to dysfunction of apically located transporters and to decreased activity of the sodium–potassium ATPase, both of which are related to structural changes in the phospholipid bilayer of the cell membrane.[18,19] In addition, excretion of renal phosphate is increased in patients with metabolic acidosis caused by increased mobilization of phosphate from bone and a direct gating effect of pH on the NaPi-2a and NaPi-2c cotransporters in the proximal tubule.[20] These abnormalities often resolve over several weeks of alcohol abstinence.[17]

Decreased reabsorption of phosphate can also be due to the action of increased levels of

Table 1. Characteristics of Alcohols Ingested in Patients with Chronic Alcohol-Use Disorder.

Alcohol	Acid–Base Disturbances and Other Features	Osmolar Gap	Treatment
Ethanol	Mixed disturbances (including anion-gap acidosis, normal-gap acidosis, and respiratory and metabolic alkalosis) common	Increased by 11 mOsm per kilogram per change of 50 mg per deciliter in alcohol concentration	5% dextrose in 0.9% (normal) saline; benzodiazepines to prevent alcohol withdrawal
Ethylene glycol	Anion-gap metabolic acidosis in association with acute kidney injury and calcium oxalate crystals in urine	Increased by 8 mOsm per kilogram per change of 50 mg per deciliter in alcohol concentration	Administration of fomepizole to inhibit alcohol dehydrogenase and limit formation of toxic metabolites; hemodialysis
Methanol	Anion-gap metabolic acidosis in association with toxic effects in the eye that may cause blindness	Increased by 16 mOsm per kilogram per change of 50 mg per deciliter in alcohol concentration	Administration of fomepizole to inhibit alcohol dehydrogenase and limit formation of toxic metabolites; hemodialysis
Isopropanol	No acidosis; positive urine and plasma ketones due to presence of acetone	Increased by 8 mOsm per kilogram per change of 50 mg per deciliter in alcohol concentration	Conservative management

circulating parathyroid hormone, the result of hypocalcemia caused by vitamin D deficiency. Magnesium deficiency can also be a cause of phosphaturia. Experimental data indicate that selective magnesium deficiency can lead to marked reductions in skeletal-muscle phosphate content and increases in excretion of urinary phosphate.[21] Furthermore, magnesium deficiency can cause a state of functional hypoparathyroidism, and in such patients, renal resistance to the effects of parathyroid hormone can increase plasma phosphate levels and cause an increase in the filtered load of phosphate, thereby contributing to inappropriate phosphaturia.

Unmasking of the total-body deficit in phosphorus after hospital admission is multifactorial. Normalization of pH in patients with ketoacidosis will cause an intracellular shift of phosphate. Increased intracellular pH stimulates the rate-limiting enzyme for glycolysis, necessitating cellular phosphate uptake in order to phosphorylate glucose, since intracellular stores are depleted. Release of insulin after administration of glucose-containing fluids will exacerbate this shift. In patients who have alcohol withdrawal, the development of respiratory alkalosis and increased levels of circulating catecholamines provide additional stimulatory effects for the uptake of cellular phosphate.

Hypophosphatemia leads to a variety of manifestations that may include weakness in the skeletal muscles and rhabdomyolysis, which are probably due to the presence of an underlying ethanol-induced myopathy. In muscle-biopsy samples obtained from patients with chronic alcohol-use disorder and from dogs that have received alcohol, there are significant reductions in phosphate and magnesium content in skeletal muscles; these reductions are accompanied by increased amounts of sodium and chloride and a greatly increased calcium content[22-24] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In patients with hypophosphatemia who have been abusing alcohol, a sudden decrease in the plasma phosphate level explains the increased frequency of acute rhabdomyolysis during alcohol withdrawal. The absence of rhabdomyolysis in healthy persons who hyperventilate or in patients treated for diabetic ketoacidosis in whom a rapid decrease in plasma phosphate levels also develops suggests that underlying muscle injury is required for the development of this complication and is unique to persons with chronic alcohol-use disorder.

Hypophosphatemia also contributes to the development of metabolic acidosis. Intracellular deficiency of phosphate impairs generation of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Decreased cellular ATP stimulates phosphofructokinase activity, enhancing glycolysis and lactate production. In red cells,

cellular phosphate deficiency lowers the content of 2,3-diphosphoglycerate, and reductions in the level of 2,3-diphosphoglycerate increase the affinity of hemoglobin for oxygen by shifting the oxygen disassociation curve to the left, thereby predisposing the patient to tissue ischemia and increasing lactic acid production. As phosphate shifts into cells, levels of urinary phosphate decrease, reducing the buffering capacity of the kidneys for hydrogen ion secretion, although this effect tends to be mild.

MAGNESIUM AND CALCIUM DISTURBANCES

Hypomagnesemia occurs in almost one third of patients with chronic alcohol-use disorder.[17,25] In acutely ill hospitalized patients, the plasma magnesium concentration typically decreases from normal or only slightly reduced values to severely reduced levels over several days, unmasking total-body depletion of magnesium (Table 2). Decreased body stores of magnesium result from insufficient consumption of magnesium-enriched foods, such as green leafy vegetables, nuts, and meats. In addition, gastrointestinal absorption is decreased in patients with chronic diarrhea or steatorrhea, the latter of which causes the formation of fatty acid–magnesium complexes. Losses of renal magnesium are present owing to reversible ethanol-induced tubular dysfunction. Although selective magnesium deficiency can lead to renal phosphate wasting, the reverse is also true. Selective depletion of phosphate from skeletal muscle leads to reductions in the magnesium and ATP content in muscle; this accounts for the frequent coexistence of these disorders.[22-24]

The development of hypomagnesemia after admission to the hospital is due to the intracellular shift brought about by correction of acidosis and administration of glucose-containing fluids leading to insulin release. Increased catecholamines and respiratory alkalosis accompanying alcohol withdrawal also contribute to the intracellular shift.

The clinical manifestations of hypomagnesemia are primarily neuromuscular irritability manifested by weakness, tremors, and a positive Trousseau's sign. Magnesium depletion suppresses release and induces peripheral resistance to parathyroid hormone; this explains the persistence of hypocalcemia until the magnesium deficit is repaired. Hypocalcemia will correct in minutes to hours after the restoration of normal concentrations of plasma magnesium. Residual high plasma concentrations of ethanol also limit the hypercalcemic response to parathyroid hormone.

Vitamin D deficiency should be considered as a contributing factor in patients with hypocalcemia. Risk factors include poor dietary intake of vitamin D, lack of exposure to sunlight, and direct effects of alcohol on vitamin D metabolism or decreased absorption in patients with alcohol-related steatorrhea. Rhabdomyolysis can cause hypocalcemia owing to the deposition of calcium phosphate in injured muscle tissue.

POTASSIUM DISTURBANCES

Hypokalemia occurs in nearly 50% of hospitalized patients with chronic alcohol-use disorder.[17,26] As with magnesium and phosphorus, plasma potassium concentrations may be normal or only slightly reduced on admission, only to decrease over several days because of an inward cellular shift that unmasks decreased total-body stores. Potassium deficiency results from inadequate intake and gastrointestinal losses due to diarrhea. Urinary losses also contribute and are multifactorial. Vomiting and ketoacidosis lead to increased loss of urinary potassium that is due to the coupling of increased mineralocorticoid levels and increased delivery of sodium to the distal nephron (Table S2 in the Supplementary Appendix). Increased sodium delivery is due to the nonreabsorbable anion effect of bicarbonate in patients with vomiting and of ketoacid salts in patients with alcoholic ketoacidosis.[27]

Coexistent magnesium deficiency also causes inappropriate kaliuresis. Under normal circumstances, intracellular magnesium blocks the ROMK channels, which are located on the apical membrane of the distal nephron and limit outward potassium secretion from the distal tubular cells.[28] Magnesium deficiency reduces intracellular magnesium, which releases the magnesium-mediated inhibition of ROMK channels, thus accounting for potassium wasting.

Stimulation of β_2-adrenergic receptors in skeletal muscle because of autonomic hyperactivity

Table 2. Electrolyte Disturbances in Chronic Alcohol-Use Disorder.*

Disturbance	Mechanism or Cause	Comment	Treatment
Acid–base			
Alcoholic ketoacidosis	Anion-gap metabolic acidosis due to decrease in insulin:glucagon ratio	Increased NADH:NAD ratio favors formation of β-hydroxybutyric acid	Administer 5% dextrose in 0.9% (normal) saline and treat other disorders if present
Lactic acidosis	Increased NADH:NAD ratio due to ethanol metabolism	Average lactate level 3 mmol per liter; consider sepsis or thiamine deficiency with higher levels	Administer 5% dextrose in 0.9% (normal) saline and treat other disorders if present
Hyperchloremic normal-gap metabolic acidosis	Indirect loss of bicarbonate due to loss of ketoacid salts in urine	Regeneration of bicarbonate by kidneys repairs deficit	Provide conservative management
Metabolic alkalosis	Vomiting	Increase in anion gap greater than decrease in bicarbonate concentration when combined with alcoholic ketoacidosis	Restore volume of extracellular fluid with chloride-containing fluids, correct hypokalemia
Respiratory alkalosis	Alcohol withdrawal, chronic liver disease, pain, sepsis	Often the primary disorder in a mixed acid–base disturbance	Administer benzodiazepines for alcohol withdrawal; treat underlying disorders
Hypophosphatemia	Alcohol-induced urinary loss, magnesium deficiency, acidemia, increased parathyroid hormone level, nutritional deficiency, decrease in gastrointestinal absorption, cellular shift due to insulin release, respiratory alkalosis, β_2-adrenergic stimulation	Muscle weakness, rhabdomyolysis, tissue ischemia, hemolysis, cardiac dysfunction; urine phosphate excretion >100 mg/24 hr or fractional excretion ≥5% indicates renal wasting	Oral supplements preferred; for complications, administer 42–67 mmol phosphate over 6–9 hr, not to exceed 90 mmol/day to avoid decrease in calcium and magnesium levels
Hypomagnesemia	Alcohol-induced urinary loss, phosphate deficiency, nutritional deficiency, decreased gastrointestinal absorption, cellular shift due to insulin release, respiratory alkalosis, β_2-adrenergic stimulation	Persistent renal wasting can last several weeks, accounting for recurrence of hypomagnesemia after initial correction; urinary magnesium excretion >25 mg/24 hr or fractional excretion >2% indicates renal wasting	Oral supplements preferred; intravenous magnesium indicated in patients with arrhythmias or neuromuscular irritability
Hypocalcemia†	Decrease in parathyroid hormone level and resistance due to magnesium deficiency, alcohol-induced urinary loss, vitamin D deficiency	Correct for a low albumin concentration as follows: corrected calcium=serum calcium in mg/dl +[0.8×(4.0−serum albumin in g/dl)]; bicarbonate therapy can decrease ionized fraction	Correct the magnesium deficit; correct the deficiency in vitamin D
Hypokalemia	Urinary loss due to coupling of increased distal sodium delivery and increased aldosterone level, magnesium deficiency, diarrhea, cellular shift due to insulin release, correction of acidosis, respiratory alkalosis, β_2-adrenergic stimulation	A low or normal potassium level in patients with rhabdomyolysis suggests significant underlying total-body deficit of potassium; urinary potassium >30 mmol/24 hr or urinary potassium:creatinine ratio >13 (in millimoles of potassium per gram of creatinine) indicates renal wasting	Oral supplements preferred; for complications, administer intravenous potassium chloride at 10–20 mmol/hr; administer potassium before bicarbonate in patients with acidemia
Hyponatremia	Increased release of vasopressin due to volume depletion‡; decreased solute excretion in beer potomania	Increased risk of osmotic demyelination	Restore volume and increase protein intake; limit rate of correction to 6–8 mmol in first 24 hr, to slow rate with 5% dextrose in water, desmopressin, or both

* To convert the values for phosphate to millimoles per liter, multiply by 0.3229. NAD denotes oxidized nicotinamide adenine dinucleotide.
† Hypercalcemia can be present in patients with volume contraction and quickly resolves after volume resuscitation.
‡ Baroreceptor-independent factors leading to increased vasopressin may be present. These factors include pain, nausea, and the use of medications such as selective serotonin reuptake inhibitors.

and increased pH due to respiratory alkalosis contribute to the development of hypokalemia after admission to the hospital. Insulin release also contributes to the intracellular shift, an effect that is independent of glucose transport. Coexistent phosphate depletion limits insulin release in response to glucose, attenuating the effect on potassium.

The most serious manifestation of hypokalemia is cardiac toxicity, which ranges from asymptomatic electrocardiographic changes to potentially life-threatening arrhythmias. Skeletal-muscle toxicity and acute myopathy can occur and are characterized by severe weakness without muscle pain, tenderness, or swelling. Patients with chronic alcohol-use disorder often have severe hypokalemia, and many symptoms resolve after potassium repletion.[29] However, binge drinking can precipitate acute rhabdomyolysis, which is heralded by the abrupt onset of muscle pain, swelling, and weakness associated with marked elevation of plasma creatine kinase levels and myoglobinuria. In such patients, skeletal-muscle necrosis and subsequent release of potassium is a common cause of hyperkalemia. Normal plasma potassium concentrations in patients with rhabdomyolysis should arouse suspicions that depletion of total-body potassium is the underlying cause.

TREATMENT OF PATIENTS WITH MULTIPLE ELECTROLYTE DEFICIENCIES

The interplay in phosphorus, magnesium, calcium, and potassium homeostasis in hospitalized patients with chronic alcohol use explains why some, if not all, of these electrolytes are depleted (Fig. 2). Management should focus on providing oral supplementation of the relevant electrolytes whenever possible (Box 2).

Oral preparations of sodium and potassium phosphate containing 30 to 80 mmol of phosphate can be administered daily in divided doses, and they can be supplemented with milk, which is an excellent source of calcium and potassium and contains approximately 35 mmol per liter of phosphorus. Intravenous phosphate repletion may be necessary in patients who have life-threatening manifestations of hypophosphatemia (including muscle weakness, rhabdomyolysis, respiratory failure, and hemolytic anemia) and in those with severe reductions in the plasma phosphate concentration (<1.0 mg per deciliter [<0.32 mmol per liter]). In such patients, administration of 42 to 67 mmol of phosphate over a 6-to-9-hour period, but not exceeding 90 mmol per day, is appropriate.[30,31]

Close monitoring is required, since intravenous phosphate therapy can be complicated by clinically symptomatic hypocalcemia. This risk is magnified among patients with hypomagnesemia, in whom suppressed parathyroid hormone release removes a defense against further decreases in the level of calcium. An initial therapy in patients with multiple electrolyte deficiencies is a solution of 1 liter of 5% dextrose in 0.45% saline to which is added 20 mmol of potassium phosphate and 4 ml of 50% magnesium sulfate (8 mmol of magnesium) administered over a period of 8 hours. When magnesium is administered intravenously, only a small portion of each dose is retained, and most is excreted in the urine, since the renal threshold for magnesium excretion is close to the normal plasma concentration. For this reason, as well as the persistent renal leak due to effects of alcohol that last several weeks, repeated oral dosing may be required to repair the total-body deficit.

DYSNATREMIAS

Acute ingestion of alcohol induces a water diuresis owing to suppression of circulating vasopressin levels, predisposing patients to dehydration and hypernatremia.[32,33] This suppressive effect is absent with repeated exposure or prolonged continuous exposure. In these patients, vasopressin levels increase, resulting in increased urine osmolality and decreased clearance of free water. As a result, hyponatremia is a common disorder that occurs in as many as 17% of patients with chronic alcohol-use disorder.[34] Increased levels of vasopressin result from factors that override the inhibitory effect of alcohol such as increased plasma osmolality, nausea, pain, and decreased effective circulatory volume.

The approach to hyponatremia in patients with chronic alcohol-use disorder is no different from that used in other patients. Successful evaluation of the patient requires knowing whether hyponatremia indicates a hypo-osmolar state, determining whether the ability of the kidneys to dilute urine is intact, and assessing the volume status of the patient.[35] Since alcohol consumption is associated with elevated levels of plasma triglycerides, pseudohyponatremia must

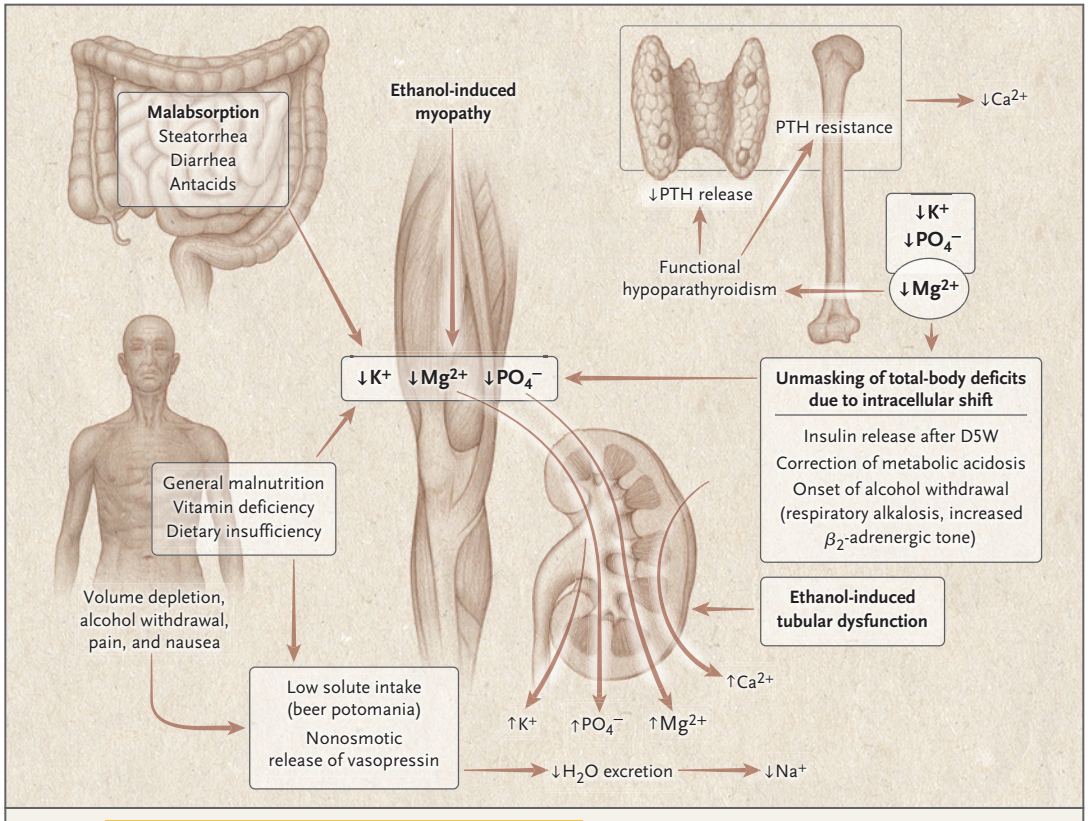

Figure 2. Total-Body Deficits in Chronic Alcohol-Use Disorder.

Patients with chronic alcohol-use disorder may have total-body deficits of phosphate, potassium, magnesium, and calcium owing to nutritional deficiencies and decreased gastrointestinal absorption, as well as tubular dysfunction due to chronic alcohol exposure. On clinical presentation, these deficits are revealed as a result of intracellular shift due to increased adrenergic tone and development of respiratory alkalosis, which characterize the onset of alcohol withdrawal, release of insulin after administration of glucose-containing fluids, and correction of metabolic acidosis. Tubular dysfunction can last several weeks after abstinence; this explains the redevelopment of hypomagnesemia and other electrolyte disorders after normalization of plasma values with supplementation in the first several days after hospitalization. Low solute intake and nonosmotic release of vasopressin account for hyponatremia in these patients. D5W denotes 5% dextrose, and PTH parathyroid hormone.

be ruled out; however, clinically significant pseudohyponatremia would be a consideration only with triglyceride levels greater than 1500 mg per deciliter (17 mmol per liter).

Beer potomania refers to a vasopressin-independent mechanism of hyponatremia in persons who drink large quantities of beer without adequate food intake. Low excretion of urinary solute limits excretion of renal water, since solute excretion determines the upper limits for the volume of renal water loss.[36] Beer has a very low sodium and protein content, and unless it is ingested with food, it provides little solute for excretion in the urine.

Laboratory findings in patients with beer potomania include severe hyponatremia (plasma sodium concentration, <110 mmol per liter),

Box 2. A 42-year-old woman is admitted to the hospital with a history of several weeks of increasing weakness and fatigue followed by the onset of paresthesias in the legs 1 week before admission.

She normally drinks up to 1 pint of vodka per day but has not ingested any alcohol over the past 24 hours. Vital signs on admission show a blood pressure of 134/82 mm Hg and a pulse rate of 110 beats per minute and no orthostatic changes. The respiratory rate is 24 breaths per minute, and she is afebrile. Physical examination shows a disheveled woman who appears visibly agitated. Her laboratory values are as follows: sodium, 140 mmol per liter; potassium, 2.4 mmol per liter; chloride, 103 mmol per liter; bicarbonate, 21 mmol per liter; creatinine, 1.2 mg per deciliter (106 μmol per liter); blood urea nitrogen, 35 mg per deciliter (12.5 mmol per liter); calcium, 6.5 mg per deciliter (1.62 mmol per liter); magnesium, 0.6 mg per deciliter (0.24 mmol per liter); phosphate, 1.5 mg per deciliter (0.48 mmol per liter); and albumin, 3.8 g per deciliter. A measurement of arterial blood gas obtained while the patient was breathing ambient air showed a pH of 7.50, a partial pressure of carbon dioxide of 28 mm Hg, and partial pressure of oxygen of 110 mm Hg. The acid–base disturbance and the type of fluid therapy that is appropriate for correction of the underlying disorders are noted in Case 2 in the Supplementary Appendix.

Box 3. A 52-year-old man who typically drinks 15 to 20 beers per day presents to the emergency department with a history of nausea over the past 48 hours.

He has had no food intake over the past 2 days but has continued to drink the same amount of beer each day. On physical examination, he has difficulty following commands. His laboratory values on admission are as follows: sodium, 110 mmol per liter; chloride, 78 mmol per liter; potassium, 3.9 mmol per liter; bicarbonate, 22 mmol per liter; creatinine, 0.7 mg per deciliter (62 μmol per liter); blood urea nitrogen, 4 mg per deciliter (1.4 mmol per liter); spot urinary sodium, 12 mmol per liter; and urine osmolality, 234 mOsm per kilogram of water. He receives thiamine followed by 1 liter of 5% dextrose in 0.9% normal saline. The urine output during the first 5 hours after presentation is 3.2 liters. The acid–base disturbance and the type of fluid therapy that is appropriate for correction of the underlying disorders are noted in Case 3 in the Supplementary Appendix.

hypokalemia, low blood urea nitrogen levels (indicating low protein intake), and a maximally dilute urine (<100 mOsm per kilogram of water). In some patients, the urine osmolality may be higher than 100 mOsm per kilogram owing to coexistent nonosmotic release of vasopressin caused by volume depletion, alcohol withdrawal, nausea, or medications (see Box 3).

Administration of solute, either as sodium chloride in intravenous fluids or refeeding combined with fluid restriction, typically results in a brisk diuresis in patients with beer potomania. Rapid correction of the ensuing hyponatremia is problematic because osmotic demyelination occurs in approximately 18% of patients.[37] Hypokalemia and hypophosphatemia are risk factors for this complication.[38,39] To minimize the risk, the therapeutic goal is to limit correction of the plasma sodium level to between 4 and 6 mmol in a 24-hour period.[40] Administration of 5% dextrose in water, administered either with or without desmopressin, slows the rate of correction and, if needed, can be used to lower the plasma sodium level again in patients in whom overcorrection has already occurred.

CONCLUSIONS

An array of acid–base disorders and electrolyte disorders can occur in patients with chronic alcohol-use disorder, irrespective of their social circumstances. Thus, these disorders are not confined to unfortunate patients with malnutrition and intercurrent illness, but rather they can be encountered in well-nourished patients who are abusing alcohol, since alcohol ingestion itself is directly involved in the underlying pathophysiological features of these derangements.

Treatment of the underlying cause of hospital admission will unmask the disturbances that have been described in this review. Furthermore, electrolyte disturbances that are present may be corrected initially, but owing to the deleterious effects of alcohol on renal tubular function, they may reappear within days after the initial correction. Understanding the pathophysiological features of electrolyte disorders related to alcohol abuse should help physicians to implement appropriate therapies and avoid the potential toxic effects of these abnormalities in their patients.

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

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