

Metabolic Abnormalities in Alcoholic Patients: Focus on Acid Base and Electrolyte Disorders

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Abstract

Alcoholic patients commonly develop a variety of acid-base and electrolyte disturbances. The aim of this review is to describe the most commonly encountered abnormalities and their significant role in the patients' morbidity and mortality. Physicians should be aware of these clinically important disturbances caused by alcohol abuse and their underlying pathophysiological mechanisms involved for their appropriate management.

Alcoholic Keto Acidosis (AKA) is a medical emergency is more common than previously thought and is characterized by an increased anion gap metabolic acidosis. However, in AKA mixed acid-base disorders are commonly observed. Alcoholic patients also exhibit severe electrolyte derangements. Multifactorial origin hypomagnesaemia is the most common electrolyte abnormality observed. Hypocalcaemia is also a frequent electrolyte disturbance and is commonly associated with hypomagnesaemia. Hypokalemia is occasionally encountered in these patients, while multifactorial origin hypophosphatemia is the second common electrolyte abnormality found. Hyponatremia is also a common electrolyte derangement and may occur subsequent to several mechanisms mediated by alcohol toxicity. Of special interest is the so-called beer potomania syndrome in poor nourished patients who consume a large amount of water with beer leading to hyponatremia. Chronic alcoholism and its comorbidities are a predisposing factor for the development of Central Pontine Myelinolysis during rapid correction of hyponatremia. Occasionally, alcoholic patients could be presented with alcohol-related intoxication mainly due to simultaneous methanol or ethylene glycol intoxication. In these cases the determination of the serum osmolal gap is used as a screening tool to identify potential toxins.

Keywords: Alcoholism; Acid-base disturbances; Electrolyte disturbances

Introduction

Alcoholism is a major issue globally. It is estimated to be the fifth leading risk factor for global disability-adjusted life years. Alcohol consumption in the United States is rising and between 22% and 26% of US community hospital admissions are alcohol related [1]. Alcohol dependence and alcohol abuse cost the United States US\$220 billion in 2005.

Commonly chronic alcoholic patients develop a variety of acid-base and electrolyte disturbances, which play a significant role in their morbidity and mortality. Physicians should recognize these abnormalities and the underlying interrelated pathophysiological mechanisms for their prompt diagnosis and appropriate management. Thus, in this detailed review of acid-base and electrolyte abnormalities in alcoholic patients a careful analysis of these disturbances is attempted taking into account the extensive experience of our center in this topic.

Alcoholic Keto Acidosis and Mixed Disorders

In chronic alcohol misusers following an abrupt cessation or reduction of alcohol consumption a condition usually identified is Alcoholic Keto Acidosis (AKA), a poorly diagnosed medical emergency and a common reason for investigation and admission to the emergency departments. AKA is more common than previously thought. In an autopsy study of alcoholics it was the cause of death in 7% of cases [2].

The main predisposing events for the development of AKA are insulin deficiency and glucagon excess, which seems to be caused by: a) starvation and glycogen depletion, b) extracellular

fluid volume depletion, and c) Nicotinamide Adenine Dinucleotide hydrogenase (NADH)/Nicotinamide Adenine Dinucleotide (NAD) ratio elevation secondary to alcohol metabolism by alcohol dehydrogenase [3].

In alcoholic patient's dehydration and acute starvation suppress insulin, increase ketogenesis and the secretion of counter regulatory hormones, such as catecholamine's, cortisol, growth hormone and glucagon. The latest can increase the release of fatty acids which are metabolized to beta-hydroxybutyrate and acetoacetic acid. The raised ketoacids resulted in an increased anion gap metabolic acidosis.

Clinical symptoms, such as nausea, intractable vomiting, abdominal pain, and altered mental status are by far the most common manifestations in AKA. Likewise, the most frequent physical findings include tachycardia, tachypnea and abdominal tenderness [3,4]. On the other hand signs of significant abdominal distention, decreased bowel sounds, ascites or rebound tenderness are rarely reported. In AKA altered mental status, abnormalities in

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orientation or level of consciousness could be also seen. However, a process other than AKA that could explain the altered mental status, such as hypoglycemia, severe alcohol intoxication or stroke should be carefully excluded.

Common laboratory results are metabolic acidosis with a raised anion gap as well as normal or low glucose level, low or absent blood alcohol levels and urinary ketones [3,4]. In about 50% of these patients serum amylase is raised [4]. In an alcoholic patient with metabolic acidosis a high anion gap along with normal serum lactate levels may be an important clue for the diagnosis of AKA, which may be missed because the nitroprusside test widely used to assess ketonuria reacts only with acetoacetate, and not with β -hydroxybutyrate, the primary ketoacid seen in AKA. In these cases a direct assay for the determination of β -hydroxybutyrate in serum should be used. The latest is preferred also for monitoring response to therapy. On the other hand, the addition of hydrogen peroxide in a urine sample can transform β -hydroxybutyrate to acetoacetate which is easily assessed by a dipstick with nitroprusside test.

It has been mentioned that concomitant metabolic alkalosis from combined effects of volume contraction and vomiting or respiratory alkalosis from alcohol withdrawal, pain, high temperature, liver disease, sepsis or pregnancy may lead to a normal or even elevated arterial pH in individuals with AKA [5,6].

Thus, even though AKA is typically characterized by a high anion gap metabolic acidosis, mixed acid-base disorders are commonly observed (Table 1). Firstly, the four types of metabolic acidosis seen in AKA, emphasized by Halperin et al. are pure ketoacidosis, coexistent alcohol-induced lactic acidosis, acetic acidosis and also hyperchloremic acidosis probably as the result of “indirect” loss of bicarbonate in the urine as sodium β -hydroxybutyrate is rapidly metabolized to bicarbonate [3]. Secondly, as previously mentioned other acid-base disorders are commonly encountered in this population. In fact Wrenn et al showed that only 55% of the patients are acidemic and 78% had a mixed acid-base disorder [4]. Additionally, Fulop et al noted the complexity of the acid-base disorders because half of their patients were not acidemic and almost one third was actually alkalemic [4-7].

AKA may be difficult to differentiate from diabetic ketoacidosis when blood glucose values are higher than 13.8 mmol/L (250 mg/dl). Of note, hyperglycemia has been noted in 35% of patients with alcoholic ketoacidosis [8]. In diabetic ketoacidosis, a history of alcohol abuse can contribute to the development of ketoacidosis decreasing further the level of insulin. In these patients a coexistent pancreatitis can also contribute to the development ketoacidosis [9].

Alcoholic ketoacidosis	
A high anion gap metabolic acidosis	Coexistent acid-base disorders
Pure ketoacidosis	Metabolic alkalosis [due to volume contraction and vomiting]
Lactic acidosis	Respiratory alkalosis [due to alcohol withdrawal, pain, sepsis or liver disease]
Acetic acidosis	
Hyperchloremic acidosis [due to “indirect” loss of bicarbonate in the urine]	

Table 1: Acid-base derangements in alcoholic patients.

Other important differential diagnoses are alcohol-induced lactic acidosis, which can be diagnosed by the determination of serum lactate levels, but also salicylate, methanol or ethylene glycol poisoning. Awareness of the syndrome, a thorough medical history, a careful physical examination and routine laboratory analyses can usually lead to a correct diagnosis of AKA [8].

Rehydration and carbohydrates supply with dextrose and saline solutions is the essential management of AKA, which has a rapid response to treatment. Intravenous thiamine should be given routinely along with attention to concomitant clinical problems. Electrolyte abnormalities should be carefully monitored and corrected. Insulin or alkali should be avoided [5,7-10].

Electrolyte Abnormalities

Hypomagnesaemia

In long-term alcoholics hypomagnesaemia is the most common electrolyte abnormality observed. It is the result of various pathophysiologic mechanisms [11,12] (Table 2). In one study in a large group of alcoholic patients admitted to our university hospital for causes related to alcohol abuse, hypomagnesaemia was the most common electrolyte disturbance observed in 38 of the 127 patients (29.9%)[13]. In particular, the mean (SD) total magnesium levels was 0.7 ± 0.2 mmol/L, which was significantly lower than that observed in the 203 normal controls (0.9 ± 0.3 mmol/L, $p < 0.001$) [13]. The underlying pathogenic mechanisms of hypomagnesaemia in alcoholic patients include:

a) Increased renal losses of Mg^{2+} caused by coexistent metabolic acidosis[8], hypophosphatemia [14,15] as well as by a direct magnesiuric effect of acute alcohol consumption [13-17]. Furthermore, magnesiuria could be the result of transient hypoparathyroidism reported during alcohol intoxication. This decline in the secretion of parathyroid hormone might enhance renal magnesium excretion concordantly with a deterioration of the coexistent hypocalcaemia [18]. Additionally, in a well-designed study, reversible ethanol-induced defects in renal tubular function were suggested as responsible for the enhanced urinary magnesium and other electrolytes excretion [14].

b) Decreased magnesium intake, which may play a significant role in the pathogenesis of hypomagnesaemia in poorly nourished alcoholics.

c) An increased magnesium entry into the cells mainly due to the coexistent respiratory alkalosis. Furthermore, an excessive catecholamine release caused by alcohol withdrawal syndrome [11] may also result in the transfer of magnesium into the cells.

d) Increased gastrointestinal magnesium losses due to diarrhea or steatorrhea may also play a role in the development of hypomagnesaemia in some patients[11].

In alcoholic patients with hypomagnesaemia other clinically important electrolyte disturbances have been well described [12]. In fact, reversible hypocalcaemia is commonly found in these patients [19]. In patients with severe hypomagnesaemia (serum $Mg^{2+} < 1$ mEq/L) the hypocalcemia may be the result of reduced PTH secretion or the resistance to the action of PTH [20]. Thus, the detection of hypocalcemia is thought to be a reasonably accurate predictor of the coexisting hypomagnesaemia [15]. On the other hand, hypomagnesaemia ultimately promotes inappropriate kaliuresis, thus resulting in hypokalemia [21]. It

is well known that hypomagnesaemia of any case can lead to potassium depletion caused by both urinary and fecal losses. The inappropriate kaliuresis mainly reflects impaired proximal tubular reabsorption of potassium and increased distal tubular secretion [22,23]. The exact tubular defects accounting for the inappropriate kaliuresis have not been determined. Restoration of potassium alone is usually ineffective because the exogenous potassium is excreted in the urine rather than being taken by the cells [23,24]. In this regard, magnesium is required for the normal activity of the Na⁺-K⁺-ATPase pump, responsible for the active transport of potassium into the cells. The correlation between serum potassium and magnesium levels as well as between serum magnesium levels and potassium excretion in alcoholic patients with hypokalemia strengthen the importance of hypomagnesaemia in the development of hypokalemia [11-23,24].

In stable hospitalized patients it is proposed that correction of hypomagnesaemia can be achieved with the administration of 32-64 mEq Mg²⁺ in 12-24 h in patients with serum Mg²⁺ levels <0.8 mEq/L, 16-32 mEq/L in 6-12 h in patients with serum Mg²⁺ levels < 0.8-1.2 mEq/L and 8-16 mEq in patients with serum Mg²⁺ levels <1.2-1.6 mEq/L [25]. However it should be noted that oral administration of magnesium for a long period of time is necessary to restore the magnesium balance in the body [25].

Hypocalcaemia

Hypocalcaemia is also a frequent electrolyte abnormality in alcoholic patients with a prevalence ranged between 5-15% [17,26]. As previously mentioned hypocalcaemia is believed to be the result of hypomagnesaemia, as reversible hypocalcaemia is frequently found in association with magnesium depletion [11,27] (Table 2). Additionally, respiratory alkalosis occasionally observed in alcoholic patients can induce renal PTH resistance resulting in hypercalciuria, hypocalcaemia and hypophosphatemia [20]. It should be mentioned that malnourished patients with hypoalbuminemia can also exhibit pseudohypocalcemia. In such cases the albumin-corrected serum calcium levels should be the estimated, since each reduction of serum albumin by 1 g/L lead to an equivalent reduction of serum Ca²⁺ by 0.8 mg/dl. In chronic alcoholic patients calcium repletion is rarely needed. In most cases, magnesium repletion will usually allow spontaneous correction of hypocalcaemia [16].

Hypokalemia

It is worth mentioning that hypokalemia is occasionally encountered, especially in alcoholic hospitalized patients as well as in patients with alcoholic ketoacidosis [12,14]. In our study hypokalemia was observed in approximately 12% of the patients

[28]. The underlying mechanisms of hypokalemia in these patients are well delineated (Table 2). In most cases hypokalemia is ascribed to the coexistent hypomagnesaemia resulting in inappropriate renal potassium wasting, as previously mentioned. Additionally, in alcoholic patients with volume depletion and severe metabolic alkalosis due to vomiting an increase in the excretion of non reabsorbable bicarbonate is observed [29] and thus excess bicarbonaturia can induce high urinary potassium excretion, resulting in profound hypokalemia.

Increases potassium entry into the cells in withdrawing alcoholics due to the coexistent respiratory alkalosis and the beta-adrenergic stimulation can contribute to the development of hypokalemia [20,28-30]. In fact, in alcohol withdrawal patients the circulating epinephrine concentration increase and could produce a specific beta-2-adrenoreceptor stimulation resulting in hypokalemia [30]. It is worth mentioning that hyperinsulinemia can also contribute to the development of hypokalemia. In fact, the circulating immune reactive insulin levels are elevated in hospitalized alcoholics [31]. It is well known that insulin per se directly promotes potassium into the cells. Additionally, hyperinsulinemia is also associated with increased sympatho-excitation, which can increase the movement of potassium into cells leading to a more profound fall in serum potassium levels [32].

The treatment of hypokalemia requires the detection of the underlying causes. Since hypomagnesaemia-induced hypokalemia is resistant to replacement therapy with potassium supplements the treatment of the underlying hypomagnesaemia is necessary for the restoration of potassium balance [22-24].

In alcoholic patients with asymptomatic hypokalemia oral administration of potassium chloride/phosphate/citrate/carbonate is the treatment of choice, while in patients with severe hypokalemia (serum K⁺ <2.5-3 mEq/L) potassium should be given intravenously 20 mEq/L K⁺/2-3h [max dose 10-20 mEq/h][33].

Hypophosphatemia

Hypophosphatemia is the second common electrolyte abnormality observed in alcoholic patients [34] accounted for the 29.1% of the patients in our study [35].

Patients with chronic alcoholism commonly consume a phosphate-deficient diet which may play a role in the pathogenesis of hypophosphatemia [36]. In addition, ethanol per se induces proximal tubular dysfunction associated with decreased phosphate reabsorption and inappropriate phosphaturia, [14] as previous mentioned (Table 2). Furthermore, increased renal phosphate wasting could be due to the coexistent severe hypomagnesaemia. It has been suggested that phosphaturia is probably due to proximal

Hypomagnesemia	Hypokalemia	Hypophosphatemia	Hypernatremia	Hypocalcemia
Increased renal losses of Mg ²⁺	Kaliuresis	Phosphate deficient diet	Hypovolemia	Due to hypomagnesaemia, as well as to respiratory alkalosis leading to renal PTH resistance
Decreased Mg ²⁺ intake	Increases K ⁺ entry into the cells	Inappropriate phosphaturia	Pseudo-hyponatremia	Pseudohypocalcemia in patients with hypoalbuminemia
Increased Mg ²⁺ entry into the cells	Poor K ⁺ intake	Increased phosphate entry into the cells	Beer potomania syndrome	
Increased gastrointestinal Mg ²⁺ losses	Increased gastrointestinal K ⁺ losses	Increased gastrointestinal phosphate losses	Reset osmostat syndrome	

Table 2: Electrolyte abnormalities of alcoholic patients

tubular defect in phosphate transport [37], which is corrected with magnesium repletion. The coexistent metabolic acidosis is another important cause of hypophosphatemia, since it can increase phosphorus excretion. The precise mechanisms have not been completely elucidated [38], however metabolic acidosis can probably decrease renal cortical brush border membrane transport of phosphate in proximal tubules [39].

Increased phosphate entry into the cells is a rather common cause of hypophosphatemia and it is due to the coexistent respiratory alkalosis, to alcohol-induced hyperinsulinemia but also to increased levels of catecholamines, especially in cases of alcohol withdrawal syndrome [36,40-41].

In alcoholic patients with asymptomatic hypophosphatemia ($\text{PO}_4^{3-} < 2 \text{ mg/dl}$) oral administration of phosphorus is the treatment of choice [15-20 mg/kg body weight/d], while in patients with symptomatic hypophosphatemia ($\text{PO}_4^{3-} < 1 \text{ mg/dl}$) phosphate should be given intravenously [42]. Furthermore, dextrose solutions should not be administered because of the risk of hypophosphatemia worsening.

Hyponatremia

Hyponatremia is also a common electrolyte abnormality among chronic alcoholic patients. In a previous study 22 of 127 (17.3%) of alcoholic patients admitted to our clinic had hyponatremia with a range of serum sodium between 121 and 133 mmol/l without the presence of symptoms related to hyponatremia.

In alcoholic patients hyponatremia may occur subsequent to several mechanisms mediated by alcohol toxicity [43] (Table 2). The most important causes of hyponatremia in this population include:

a. Hypervolemia due to true volume depletion mainly caused by gastrointestinal fluid losses.

b. Pseudo-hyponatremia due to alcohol induced-hypertriglyceridemia, which is commonly associated with alcohol abuse.

c. Beer potomania syndrome: This syndrome is mostly observed in alcoholic binge drinkers. The consumption of a large amount of hypo-osmolar beer predisposes to hypo-tonicity and inhibits Anti Diuretic Hormone (ADH) release. Normally as ADH drops less water is absorbed and increase urine is produced. However kidney needs solutes and electrolytes to be processed for urine elimination. The kidneys require 50 to 60 mOsmol of solutes, to produce 1 L of maximally dilute urine. The alcoholic malnourished patients with poor dietary intake and lack of other sources of solutes do not have these available solutes to produce dilute urine. Additionally, the intake of a large amount of water with beer causes a net fluid retention and hyponatremia [43-45].

Vital signs could include generalized weakness, nausea and vomiting, muscle cramping, peripheral edema, cerebral edema, changes in mentation or memory, restlessness and irritability, gait disturbances, uncontrolled tremors, seizures and coma [43-46].

The diagnostic criteria for this syndrome are serum sodium usually less than 110 mEq/L which could not be explained from other causes, history of long-standing protein malnutrition, and consumption of a large amount of beer (usually more than fifteen 12-oz beers or 5.4 L of beer) in a relatively short time[43,44].

In these patients all the other causes of hyponatremia, such as pseudo-hyponatremia due to hypertriglyceridemia, multifactorial origin syndrome of inappropriate antidiuretic hormone secretion, hypervolemia, hypothyroidism, cerebral salt wasting, and adrenal insufficiency should be carefully excluded by the history, a thorough physical examination and appropriate laboratory investigations [45-47].

Patients usually exhibit low urine osmolality; however urine osmolality could not be uniformly low on presentation, and could be elevated by the presence of urinary ethanol, which is an effective [48,49].

Beer potomania syndrome, if not promptly recognized and managed accordingly, can cause severe morbidity and mortality mainly because of overly rapid correction of serum sodium. Indeed, in these cases a rapid increase in serum sodium with isotonic fluid administration is commonly observed. Thus, the uncontrolled normalization of sodium from brisk free-water diuresis leads to central pontine myelinolysis (CPM), a non-inflammatory demyelinating disorder affecting the pons and other regions of the central nervous system comprising common neurological complications associated with abrupt osmotic fluctuations. A balance between the dilemma of causing CPM by correcting hyponatremia too rapidly and potential brain edema if the hyponatremia is corrected too slowly should be achieved [50-52].

d) Reset osmostat syndrome: Hyponatremia as a result of the reset osmostat syndrome occasionally encountered in chronic alcoholic patients can result from abnormal osmoreceptor activity due to defective cellular metabolism. The reset osmostat syndrome is suspected in patients with persistent hyponatremia who exhibit an appropriate decrease in $U_{\text{osm}} (< 100 \text{ mOsm/kg})$ but inappropriate natriuresis ($> 40 \text{ mmol/l}$) and could be confirmed by calculating free water clearance [53,54].

It is obvious that hyponatremia in chronic alcoholics should be approached more cautiously. Treatment of hyponatremia should be accomplished according to the recent guidelines for hyponatremia [46]. Patients with severe symptoms should be treated with a single rapid infusion of 100-150 mL of 3% sodium chloride solution which can increase serum sodium levels by approximately 2 mEq/L followed by cause-specific treatment [46-55].

It should be emphasized that the rate of increase of serum sodium should be lower than 6-8 mEq/L/24h especially in oligosymptomatic patients with chronic hyponatremia [55].

Osmolal gap intoxication

Occasionally, alcoholic patients could be presented with alcohol-related intoxication due to simultaneous consumption of other alcohols, such as methanol and ethylene glycol. In such cases the determination of the osmolal gap is important for the proper diagnosis and treatment. Normal serum osmolality of 285 to 290 mOsm/L is due to sodium and its counterbalancing ions, bicarbonate and chloride, as well as glucose and urea [56,57].

The serum osmolality measured by freezing point depression is usually within 10 mOsm/L of the calculated serum osmolality[58], which can be estimated using the following equation: Calculated serum osmolality= $[(2 \times [\text{Na}^+]) + [\text{glucose, in mg/dl}]/18 + (\text{blood urea nitrogen, in mg/dl})/2.8] + [\text{alcohol in mg/dl}]/3.7]$. The osmolal gap

is then determined by subtracting the calculated osmolality from the measured osmolality. An osmolal gap below 10 mOsm per kilogram is considered to be normal, though the normal range is large (-10 to 10 mOsm per liter) [56-60].

If the calculated osmolal gap is above >20 mOsm/L the accumulation in the blood of one of the alcohols mentioned is possible. In fact, osmolal gap should be used as a screening tool to identify potential toxins. In ethylene glycol and methanol intoxication the osmolal gap will be high shortly after their ingestion. However, the wide normal range of the osmolal gap in the general population renders this test rather insensitive to small but potentially toxic concentrations of ethylene glycol and methanol [60]. Furthermore the specificity of the osmolal gap is low because it can also be found moderately elevated in some other disorders that might be considered in the differential diagnosis of alcohol-related intoxications, such as lactic acidosis, alcoholic ketoacidosis, and diabetic ketoacidosis [60]. It is worth mentioned that some of these intoxications could be accompanied with kidney dysfunction and neurologic abnormalities. In these cases starting effective treatment before any significant metabolism of methanol or ethyl alcohol has occurred is imperative. Fortunately, since both alcohols are metabolized by alcohol dehydrogenase, the patient should receive a loading dose of fomepizole, which has a great affinity and inhibits alcohol dehydrogenase and thus attenuate the metabolism of methanol and ethylene glycol to their toxic byproducts [49].

Alcohol and Central Pontine Myelinolysis (CPM)

Chronic alcoholism predispose to the aforementioned Central Pontine Myelinolysis (CPM), which is characterized by a symmetric, demyelinating lesion of the central pons and is commonly observed after a rapid correction of chronic hyponatremia [61]. In alcoholic individuals, certain predisposing factors, including alcohol associated malnutrition and hypokalemia have emerged as potential instigators [50-52, 61,62].

Clinical findings usually arise 1-7 days after overcorrection of hyponatremia. Patients begins to exhibit weakness, confusion, dysarthria, dysphagia, mutism, parkinsonism, dystonia, quadriparesis, spasticity, catatonia and may progress to pseudo bulbar palsy and locked-in-syndrome [50].

The rapid correction of hyponatremia leads to shrinkage of neurons, with apoptosis and demyelination [63]. In this setting it should be also emphasized that alcohol exerts potentially toxic effects directly on the pons and thus leads to an osmotic disequilibrium [64].

Conclusion

It is fairly well established that electrolyte abnormalities and acid-base disorders caused by alcohol abuse play a pioneer role in their morbidity and mortality. Rapid recognition of all these abnormalities is of paramount importance for their appropriate management. It should be emphasized that hypomagnesaemia with its consequences (hypokalemia and hypocalcaemia) and hypophosphatemia are the most common electrolyte abnormalities observed. Furthermore hyponatremia due to beer potomania syndrome is a well-recognized unique entity which necessitates prompt diagnosis and careful management. Finally, symptomatic Alcoholic Ketoacidosis (a high anion gap metabolic acidosis) is occasionally encountered. This particular entity is commonly a

mixed acid-base disorder demanding a meticulous diagnostic and therapeutic approach.

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