REVIEW ARTICLE

Kidney injury, fluid, electrolyte and acid-base abnormalities in alcoholics

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ABSTRACT

In the 21st century, alcoholism and the consequences of ethyl alcohol abuse are major public health concerns in the United States, affecting approximately 14 million people. Pertinent to the global impact of alcoholism is the World Health Organisation estimate that 140 million people worldwide suffer from alcohol dependence. Alcoholism and alcohol abuse are the third leading causes of preventable death in the United States. Alcohol dependence and alcohol abuse cost the United State an estimated US$220 billion in 2005, eclipsing the expense associated with cancer (US$196 billion) or obesity (US$133 billion). Orally ingested ethyl alcohol is absorbed rapidly without chemical change from the stomach and intestine, reaching maximum blood concentration in about an hour. Alcohol crosses capillary membranes by simple diffusion, affecting almost every organ system in the body by impacting a wide range of cellular functions. Alcohol causes metabolic derangements either directly, via its chemical by-product or secondarily through alcohol-induced disorders. Many of these alcohol-related metabolic disturbances are increased in severity by the malnutrition that is common in those with chronic alcoholism. This review focuses on the acute and chronic injurious consequences of alcohol ingestion on the kidney, as well as the fluid, electrolyte and acid-base abnormalities associated with acute and chronic ingestion of alcohol.

Key words: Acid/base, alcoholics, alcoholism, electrolyte, kidney

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INTRODUCTION

No clear documentation of the initial preparation and use of ethyl alcohol as a beverage has been discerned though the discovery of late Stone Age beer jugs has established that as early as the Neolithic period (cir. 10,000 B.C.) primitive humans intentionally fermented grapes presumably to prepare intoxicating beverages. From Biblical times forward, grape fermentation and alcohol use have been a consistent component of societal life as recounted by Patrick CH.[1]

As employed in this article, the terms "alcoholic patient" and "alcoholism" designate the diagnoses of alcohol abuse and alcohol dependence as defined variously by investigators of the subject. No specific quantity of alcohol or frequency of alcohol ingestion has been established to connote the chronic state of being an alcoholic person. In the 19th and early 20th centuries, alcohol dependence was called dipsomania before the term "alcoholism" replaced it.[2] The term alcoholism is widely used, and was first coined in 1849 by Magnus Huss, but in medicine the term was replaced by the concepts of "alcohol abuse" and "alcohol dependence" in the 1980s Diagnostic and Statistical Manual (DSM) III.[3] (The term alcohol dependence is sometimes used as a synonym for alcoholism,[4,5] sometimes in a narrower sense) Similarly, in 1979, an expert World Health Organisation committee disfavoured the use of "alcoholism" as a diagnostic entity, preferring the category of "alcohol dependence syndrome".[6] It is characterised by compulsive and uncontrolled consumption of alcohol despite its negative effects on the drinker's health, relationships and social standing. Like other drug addictions, alcoholism is medically defined as a treatable disease.

Alcoholism and alcohol abuse are the third leading cause of preventable death in United States. It is estimated that alcohol dependence and alcohol abuse cost the United States US$220 billion in 2005. This expense amounted to more than the costs associated with cancer (US$196 billion) or obesity (133 billion). Approximately, 14 million people in United States, one in every 13 persons are addicted to alcohol, or abuse alcohol, including binge drinking.

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The World Health Organisation estimates that about 140 million people throughout the world suffer from alcohol dependence in United States and Western Europe. Components of this group of alcohol abusers include, 10-20% of men, and 5-10% of women who at some point in their lives will meet criteria for alcoholism.[6]

Alcohol has been reported to affect every organ system in the body. Following ingestion, alcohol is absorbed rapidly in unaltered form in small quantity in the mouth and oesophagus, moderate amount in the stomach and large intestine, but the major fraction of absorbed alcohol derives from the proximal part of the small intestine, reaching maximum blood concentration within about 1 hour.

Alcohol crosses capillary membrane by simple diffusion, altering a broad range of cellular functions. Body system function may undergo change due to alcohol both acutely and during chronic use of alcohol. Alcohol may cause metabolic derangement directly via its chemical by products or through alcohol-induced tissue or organ injury. While the underlying mechanism of alcohol-induced metabolic injury is clarified in some cases, in many others, it remains unknown. However, it is established that many alcohol-related metabolic derangements are made more severe by malnutrition, a common finding in chronic alcoholics.[7]

Literature reviews of the acute and chronic injurious effect of ethyl alcohol ingestion on the kidney, as well as associated fluid, electrolyte and acid-base disturbances yield highly varied and sometimes conflicting results. In this exposition, the acute and chronic injurious effects of alcohol ingestion on the kidney as well as the typical fluid, electrolyte and acid-base consequences are considered. Where available, the underlying mechanisms are detailed.

Alcohol metabolism

Alcohol is primarily metabolized in the liver to acetaldehyde in one of two ways. In the cell, cytosolic alcohol dehydrogenase employs nicotinamide adenine dinucleotide (NAD) as a cofactor to produce acetaldehyde, which is then converted to acetate by aldehyde dehydrogenase. The second pathway-microsomal alcohol oxidizing system-is clinically significant at high dose of ethanol or repeated exposure. Of the byproducts of alcohol metabolism, the most toxic is acetaldehyde. It is estimated that 10% of ingested alcohol may be excreted unchanged by the kidneys.

In long-term alcoholics, unclarified adaptations or hepatic injury may alter how these individuals handle episodic ingestion of a large amount of alcohol; consequently, microsomal alcohol oxidizing pathways may play a more significant role.

FLUID BALANCE

Acute alcohol ingestion may induce diuresis by directly inhibiting release of antidiuretic hormone (ADH) from the supraoptic-hypophyseal system.[7] Synthesis and release of ADH is a dynamic process, involving both osmotic and non-osmotic mechanisms.[7] A 1-2% change in plasma osmolality may be reflected by a change in the volume of the osmoreceptor cells located in the anterior hypothalamus. An increase in extracellular fluid (ECF) osmolality will decrease osmoreceptors cell volume and promote release of ADH. The converse is also true — ADH release is inhibited by a decrease in ECF osmolality.

Non-osmotic mechanisms that control ADH release are operative in the absence of change in ECF osmolality. They respond to severe hemodynamic changes that cause hypotension.

It has been shown that a water diuresis may be induced during the first four hours following excessive alcohol ingestion, with concomitant reduction in urine electrolyte content as a result of decreased excretion. In the next few hours following initial diuresis, small amounts of urine are produced even during continued alcohol intake.

Chronically and during recovery from alcohol ingestion, it has been noted that water is retained, and urine electrolytes excreted in greater amount than ingested. The source of these excreted ions is the ECF.

It has also been shown that the duration of an alcohol stimulus is more important than the rate of increase of alcohol level, in determining the magnitude of diuresis.[7] Slower absorption, chronically, over a longer time produces a longer diuresis from the same dose of alcohol. These observations support the hypothesis that alcohol-induced water and electrolyte diuresis result from suppression of ADH secretion from pituitary.

The immediate effect of alcohol is to cause diuresis with excretion of free water and conservation of electrolyte. This is due to suppression by alcohol of endogenous release of ADH. But, during a steady state, the reverse may be true, with alcohol acting as an antidiuretic stimulus. This is also true during chronic sustained alcohol ingestion when alcohol promotes isosmotic retention of water and electrolyte due to increased ADH levels. Excess water and electrolyte are excreted acutely with any additional alcohol ingestion. But once alcohol ingestion is discontinued, the retained water and electrolytes are usually excreted within 3-6 days.[7]

ELECTROLYTE AND ACID-BASE ABNORMALITIES

Alcoholic patients develop several electrolyte and acid-base abnormalities via multiple pathogenic

mechanisms[7-21] [Tables 1-4]. Compared to non-alcoholic subjects, chronic alcoholic patients have lower serum concentrations of potassium, magnesium, bicarbonate, calcium and phosphate as well as a lower arterial pH value.[9]

Hypomagnesaemia

Hypomagnesaemia is the most common electrolyte disturbance in alcoholics [Table 1]. The mechanisms for development of hypomagnesemia in alcoholism include, 1) increased transfer of magnesium from extracellular to intracellular fluid due to respiratory alkalosis, alcohol withdrawal syndrome with excess catecholamine release and increase gastrointestinal loss due to a chronic diarrhea syndrome. 2) Increased magnesium excretion — inappropriate magnesiuria may occur in several syndromes as in hypophosphatemia which causes a reduced magnesium reabsorption at the level of loop of Henle as well as the distal tubule, and also in acidemia resulting from diminished magnesium reabsorption in the thick ascending limb of loop of Henle.

Acute alcohol intoxication *per se*, is magnesuric,[9,10] due to either a direct effect of ethanol on tubular reabsorption of magnesium or an increased production of lactate with the potential to bind magnesium during its renal excretion. 3) Respiratory alkalosis from hyperventilation during alcohol withdrawal, with release of catecholamine. 4) Malnutrition from decrease magnesium intake.

Patients with hypomagnesaemia more frequently have hypokalaemia, hypocalcaemia, hypophosphataemia and respiratory alkalosis compared to normagnesaemia patients. Hypomagnesaemia can also lead to hypocalcaemia through a dual mechanism of impaired parathyroid hormone secretion and end organ unresponsiveness to parathyroid hormone.[8-11] Serum magnesium levels in hypomagnesaemia patients correlate well with the indices of both potassium and phosphorus excretion.

Hypokalaemia

Hypokalaemia in individuals with alcohol intoxication is thought due to inappropriate kaliuresis, as it is known that in hypomagnesaemia an inability of kidney to conserve potassium is common.[7,14,16]

Hypophosphataemia

About 50% of alcoholics who are hospitalised have hypophosphataemia.[11,17] The mechanisms for

Table 1: Acute electrolyte and acid-base abnormalities associated with alcohol intake

Hypomagnesaemia
Hypophosphataemia
Hyponatraemia
Hypokalaemia
Metabolic acidosis
Respiratory alkalosis

Table 2: Chronic electrolyte and acid base abnormalities associated with alcohol intake

Hypokalaemia
Hyponatraemia (beer potomania)
Hypomagnesaemia
Hypocalcaemia
Hypophosphataemia
Metabolic acidosis mixed with volume contracted metabolic alkalosis

Table 3: Acute and chronic kidney injury associated with alcohol intake

Acute kidney injury
Pre-renal azotemia
Myoglobinuric renal failure
Acute tubular necrosis
Chronic kidney injury
Renal tubular dysfunction
Depressed renal ammoniagenesis secondary to renal tubular damage
Hepato-renal syndrome
Moonshine nephropathy (lead toxicity)

Table 4: Acute effects of alcohol on the kidney

Electrolyte Imbalance	Mechanism	Site in Nephron
Water Diuresis	Suppression of ADH	Collecting Tubules
Hypomagnesaemia	Increased Mg Excretion, Inappropriate magnesiuria (hypophosphataemia, acidemia), Transcellular shift Respiratory alkalosis, Poor oral intake, Diarrheal loss Magnesuric effect of alcohol	Loop of Henle, Distal tubule
Hypokalaemia	Hypomagnesaemia induced inappropriate kaliuresis, Respiratory alkalosis, beta-adrenergic stimulation, Hyperinsulinaemia	Loop of Henle
Hypocalcaemia	Impaired secretion of PTH, End organ unresponsiveness to PTH	
Hypophosphataemia	Poor oral intake, Respiratory alkalosis, Hyperinsulinaemia, GI losses, Inappropriate phosphaturia	Proximal Tubules
Metabolic acidosis	Insulin deficiency with excess glucagon	Proximal tubule Thick ascending loop of Henle Distal and Collecting tubule

hyperphosphataemia in alcoholics include [Table 1] dietary phosphate deficiency, increased entry of phosphorus into cells because of hyperventilation and respiratory alkalosis, alcohol withdrawal and possibly hyperinsulinaemia and increase gastrointestinal phosphate losses.

In the case of an alcohol withdrawal syndrome, an increased level of catecholamine can cause a net shift of phosphate from ECF into the cell.

Also, inappropriate phosphaturia plays a major role in the pathogenesis of hypophosphataemia. Phosphaturia is caused by any one or combination of the following mechanisms — a) metabolic acidosis, which induces renal wasting by inhibiting proximal tubular phosphate transport,[17] b) direct inhibition of uptake by brush border membrane has also been confirmed, c) the metabolic alkalosis associated with increase phosphaturia, d) phosphaturic effect of ethanol, e) coexistence of severe hypomagnesaemia as it has been shown that phosphaturia is common in experimental magnesium depletion.[9] This is probably due to proximal tubular defect in phosphate transport.

Alcoholic ketoacidosis

Alcoholic ketoacidosis is a common disorder in chronic malnourished alcoholic patient, often describe as syndrome of wide gap metabolic acidosis.[13,22] The mechanism is complex while the main predisposing factor is relative deficiency of insulin with excess of glucagons caused by; starvation with glycogen depletion, elevated NADH/NAD ratio secondary to alcohol metabolism by alcohol dehydrogenase and extracellular volume depletion. Insulin deficiency leads to increase lipolysis and mobilization of free fatty acids. Normally, free fatty acids (FFA) carried to the liver follows one of two course:[13] 1) They are re-esterified with glycerol to form new triglyceride and subsequently very-low-density lipoprotein (VLDL) or 2) they enter the mitochondria to undergo beta-oxidation to acetate. In the absence of insulin or excess glucagons, the liver goes ketogenic. The acetate is converted to acetoacetic acid and beta-hydroxybutyric acid. Bicarbonate and other buffers buffer this organic acid. Four maim types of metabolic acidosis are seen in alcoholic ketoacidosis,[22] 1) ketoacidosis, 2) lactic acidosis, 3) acetic acidosis, 4) indirect loss of bicarbonate in the urine. Also, common are the complex interaction of the different type of metabolic acidosis with metabolic alkalosis from extracellular volume contraction.

KIDNEY INJURY

Recent animal experiment showed that prenatal exposure to ethanol could produce several renal anomalies due to toxic effect of high blood level of acetaldehyde and direct toxigenic potential of ethanol.[16,19,20] Histologically, interstitial oedema and tubular dilatation with flattening of epithelial lining cell were found. This can be explained by the effect of alcohol on the membrane that include lipid peroxidation, decrease biosynthesis of polyunsaturated fatty and changing membrane cholesterol and phospholipid.

There is strong evidence suggesting that the wide range of electrolyte and acid-base disturbance observed in alcoholics are due to tubular dysfunction[15,17] [Figures 1-3]. The most recent one indicate that ethanol interfere with the carrier function of these cell by decreasing Na+/K+ATPase activity and that acetaldehyde inhibit the activity of several enzymes causing the cell to become less efficient [Figure 2]. These lead to various observed defect which include 1) decrease in the threshold and maximal reabsorptive ability for glucose and in the renal threshold for phosphate excretion, increase in fractional excretion of β2-microglobulin, calcium and magnesium, aminoaciduria, impaired renal acidification and urinary concentrating ability, increase in the urinary excretion of N-acetyl beta D-glucosaminidase, a lysosomal enzyme from the proximal tubule and of alanine amino peptidase a brush border enzyme. These abnormalities are reversible.[11,14]

The fact that alcoholism is associated with multiple abnormalities of renal tubule involving different segment leads to the conclusion that exposure to ethanol may cause generalized tubular dysfunction. An abnormally elevated urine pH is a common finding in alcoholic and result from defect in the renal mechanism of acid secretion [Figure 3]. This disturbance includes low-grade urinary loss of bicarbonate and low excretion of titratable acid and ammonium. The limitation of urinary excretion of ammonium may reflect depressed renal ammoniagenesis due to overproduction of ketoacid and the failure to produce protein distally to titrate the ammonium. The renal tubular dysfunction is often associated with metabolic acidosis.[7,13,22] There is little doubt that the increase generation of ketoacid with impaired renal acidification played a role in the metabolic acidosis.

Electrolyte abnormalities in alcoholic can also be explained by the tubular dysfunction, since the defence against the depletion of mineral and electrolyte is the ability to reduce their loss in the kidney.[7,13,22]

But the acute renal failure associated with binge drinking seems to be due to other mechanism than tubular dysfunction. Volume depletion due to water diuresis as well as decrease sensitivity of collecting tubule to antidiuretic hormone and decrease medullar solute gradient, as seen in beer potomania, secondary to the prolonged and severe ingestion of hypotonic fluid have been suggested as mechanism underlying the renal failure.

In many of the alcoholic patient acute oliguric and non-oliguric renal failure occur due to a direct toxic effect

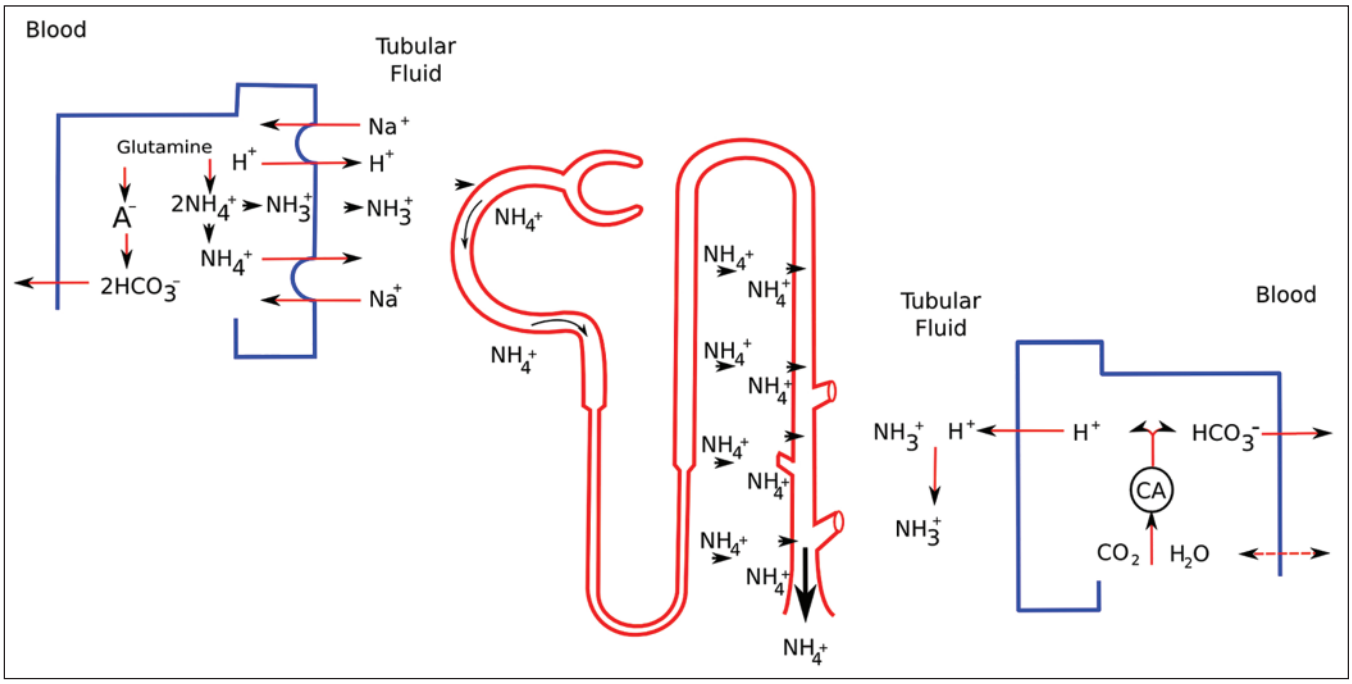

Figure 1: Impaired renal ammoniagenesis. Ammonia is synthesised in proximal tubule but concentrated in the collecting duct by process of diffusion trapping. This process is impaired in chronic alcoholics

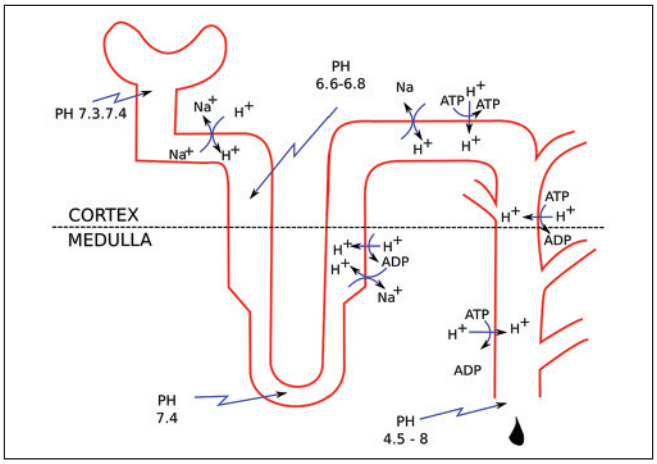

Figure 2: Impaired Acidification of urine: Na+/H+exchange (primarily proximal), H+ATPase (primarily distal and collecting tubule)

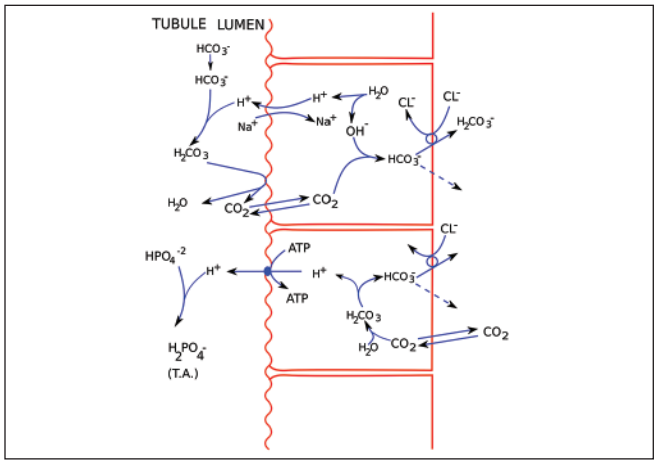

Figure 3: Impairment of titrable acid excretion. Excretion of titratable acid is impaired in chronic alcoholics resulting in the high urinary pH

of ethanol on muscle with depletion of potassium and phosphate affecting the energy production. There is also an acute blockage by the myoglobin precipitate as well as their toxic effect on the tubular cells.[19] Acute and chronic renal failure can result from consumption of illicit alcohol due mostly to contaminant mostly lead and glycol. The acute type is characterised by the proximal tubular dysfunction similar to the one seen in fanconi syndrome. But the more difficult to diagnose chronic type is a histological confirmed tubulointerstitial renal disease with fibrosis and atrophy of the renal tubules characterised by proteinuria, hypertension, gout and hyperuricemia. Alcoholic liver cirrhosis with associated hepato-renal syndrome is common complication of chronic alcohol consumption, the renal failure developed as a result of extreme splanchnic vasodilatation and compensatory renal vasoconstriction.[23,24]

CONCLUSION

Alcohol ingestion is associated with myriad of deleterious effects on the kidney ranging from tubular dysfunction and various forms of acute renal failure.

Acute ingestion of alcohol causes water diuresis due to inhibition of arginine vasopressin (AVP) release, but this effect is transient. An anti-natriuretic effect occur during chronic exposure which leads to increase sodium reabsorption by both the proximal nephron and loop of Henle, this contribute to decrease potassium secretion due to a decrease sodium delivery to the distal nephron.

Various studies propose that generalised tubular dysfunction causing reduced reabsorptive ability of tubular cell played a role in the various electrolyte abnormalities seen in alcoholics. And the increased generation of ketoacid that leads to depressed renal ammoniagenesis and thus decrease excretion of titratable acid play a major role in the pathogenesis of metabolic acidosis in alcoholic patient.

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