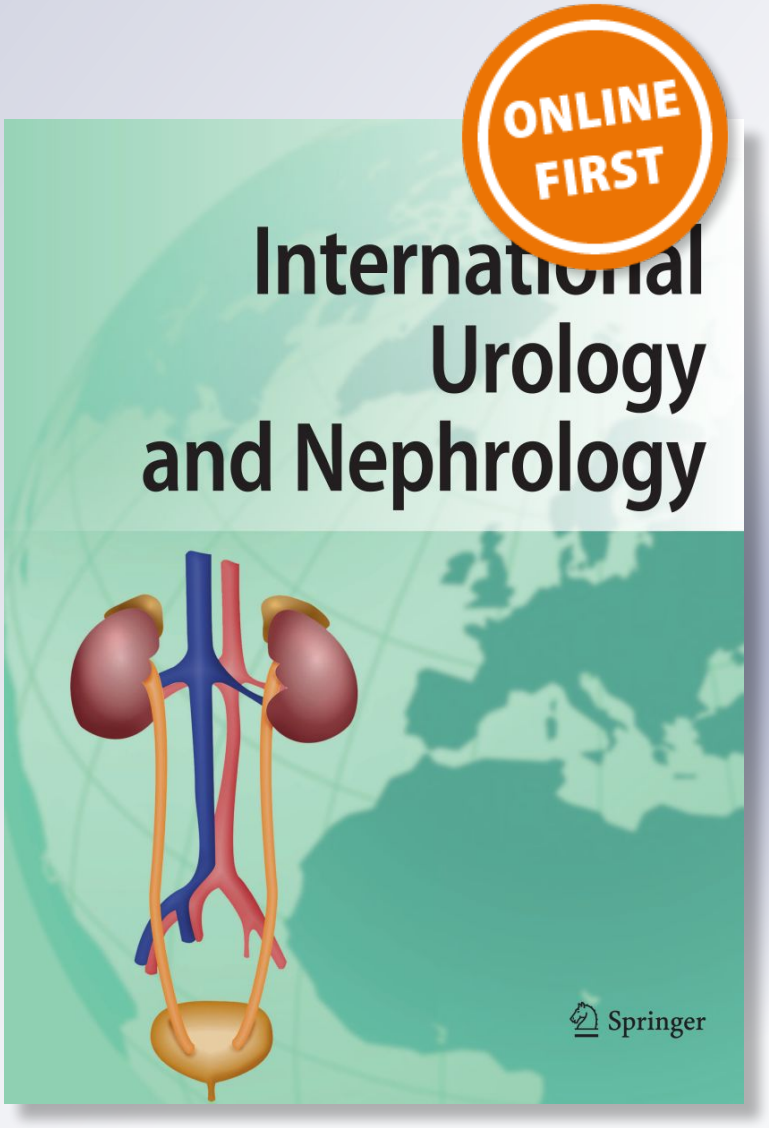
Water, electrolyte, acid–base, and trace elements alterations in cirrhotic patients

Carlos G. Musso, Rossina Juarez & Richard J. Glassock

International Urology and Nephrology

ISSN 0301-1623

Int Urol Nephrol
DOI 10.1007/s11255-017-1614-y



Springer

Int Urol Nephrol
DOI 10.1007/s11255-017-1614-y

NEPHROLOGY - REVIEW

Water, electrolyte, acid–base, and trace elements alterations in cirrhotic patients

Carlos G. Musso[1] · **Rossina Juarez**[2] · **Richard J. Glassock**[3]

Received: 15 March 2017 / Accepted: 2 May 2017

Abstract Chronic hepatic patients, and particularly those suffering from cirrhosis, are predisposed to different sort of water, electrolyte, acid–base, and trace elements disorders due to their altered liver function, and also to their exposition to infectious, inflammatory, oncologic, and pharmacologic variables whose combination undermines their homeostatic capability. Hyponatremia, hypokalemia, hyperkalemia, hypocalcemia, metabolic acidosis, respiratory, and metabolic alkalosis are the main internal milieu alterations in this group.

Keywords Cirrhosis · Electrolytes · Internal milieu · Acid–base · Trace elements

Introduction

Pathopysiological changes secondary to chronic liver disease and cirrhosis predispose these patients to develop different sorts of water, electrolyte, and acid–base alterations [1–3]. The mechanisms underlying these disorders are manifold and complex and can have significant impact on the prognosis, morbidity and mortality of this group. Cirrhotic portal hypertension leads to systemic vasodilation that reduces renal blood flow and glomerular filtration rate (GFR), reverses normal diurnal rhythm of sodium excretion, and induces sodium–water retention through the activation of renin–angiotensin–aldosterone axis and vasopressin hormone, respectively. Vasopressin increases solute-free water retention by acting on the V2 receptors of the kidney collecting tubules. However, an impaired water excretion is also present in this population due to a combination of renal hypoperfusion and low urinary solute excretion. Additionally, an impaired urinary acidification, potassium handling, as well as reduced urine concentrating capability, can be documented in cirrhosis.

Prognostic models in liver cirrhosis

Two models for assessing general prognosis in cirrhosis have been described: Child–Pugh and model for end-stage liver disease (MELD) [4]. Regarding Child–Pugh classification, it includes variables as ascites, encephalopathy, serum bilirubin, albuminemia, and prothrombin time (Table 1). The simplicity of this classification has determined its wide utilization, but since it has important drawbacks, another prognostic model (MELD) has been described. These main drawbacks are the absence of renal variables, as well as the presence of non-prognostic (prothrombin) and subjective (encephalopathy and ascites) variables [4]. The MELD scoring model currently uses international normalized ratio (INR), total serum bilirubin level, and creatininemia to predict patients' survival based on the following equation [4]: MELD = 3.8 $\log_e$ [bilirubin (mg/dL)] + 11.2 $\log_e$ [IRN] + 9.6 $\log_e$ [creatininemia (mg/dL)] + 6.4 (Table 2). However, since it has been demonstrated that to incorporate serum sodium (Na) into MELD (MELD-Na) provides more accurate survival prediction than MELD alone, this new score is currently used, which is based on the following equation [5]: MELD-Na = MELD + 1.59 (135—Na)

✉ Carlos G. Musso
carlos.musso@hospitalitaliano.org.ar

[1] Nephrology Division, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[2] Climedica Hospital, Buenos Aires, Argentina

[3] Department of Medicine, Geffen School of Medicine, UCLA, Los Angeles, CA, USA

Published online: 12 June 2017

Table 1 Child–Pugh classification

Variables	Points		
	1	2	3
Encephalopathy	Absent	I–II	III–V
Bilirubin (mg/dl)	<2	2–3	>3
Ascites	Absent	Mild	Tense
Prothrombin (%)	>50	30–50	<30
Albuminemia (g/L)	>35	35–28	<28

Group A 5–6 points (stable cirrhosis without need of transplant)

Group B 7–9 points (stable but susceptible to destabilization)

Group C ≥ 10 points (need of liver transplant)

Table 2 Three-month survival in MELD score

MELD	Three-month mortality (%)
<9	1.9–3.7
10–19	6–20
20–29	19.6–45.5
30–39	52.6–74.5
>40	71–100

with maximum and minimum Na of 135 and 120 mmol/L, respectively [5–7].

Sodium retention in liver cirrhosis

The cause of sodium retention in liver cirrhosis is primarily due to enhanced renal tubule reabsorption rather than changes in the filtered sodium load. However, different mechanisms have been proposed in order to explain this phenomenon, as follows [3, 8–12]:

Underfil theory

Portal hypertension promotes fluid transudation from the vascular system through the hepatic sinusoidal bed to the peritoneal cavity (ascites) and consequently induces effective hypovolemia. This phenomenon is the initiator of salt and water retention due to the activation of renin–angiotensin–aldosterone system, sympathetic nervous system, and non-osmotic vasopressin secretion in an attempt to restore euvolemia. As a consequence of these neuro-hormonal changes, sodium reabsorption by the proximal convoluted tubule increases from 60 to 85%, and there is also a reduction in the delivery of sodium to the thick ascending limb of Henle's loop (15% instead of 40%), and to the early distal tubule (5% instead of 9%) [13]. These functional changes result in low urinary sodium concentration (<10 mmol/lL) and low fractional excretion of sodium (<0.5%) [14]. Moreover, sympathetic overactivity induces antinatriuresis by decreasing total renal blood flow or by acting directly at the proximal tubule to enhance sodium reabsorption [15].

Overflow theory

This theory proposes that a hepatic–renal reflex is triggered by portal hypertension, causing sodium retention by the kidney, and consequently leading to intravascular expansion, and ascites formation. This theory is supported by the finding that up to 25% of cirrhotic patients with ascites do not have elevated aldosterone, renin, norepinephrine, or vasopressin serum levels. However, the fact that cirrhotic patients without ascites have "mineralocorticoid escape," a compensatory urinary sodium excretion induced by deoxycorticosterone acetate (DOCA) or natriuretic peptide, argues against this theory [2, 16, 17].

Peripheral arterial vasodilation theory

This theory attempts to unify the previous theories and proposes that there is an intravascular space compartment that enlarges in cirrhotic patients (splanchnic bed) which causes the "*underfilling*" of the arterial circulation. This vasodilatation, which is induced by endotoxins, prostaglandins, and nitric oxide, leads to low effective arterial volume (underfill), and triggers renal sodium retention [2, 3, 17]. All the above-mentioned pathophysiological changes, and several diseases usually found in cirrhotic patients, predispose them to suffer from different electrolytes disorders, whose more frequent forms are described in detail in this review.

Dysnatremias: hyponatremia and hypernatremia

Hyponatremia

The prevalence of hyponatremia is around 57 and 40% in hospitalized and ambulatory cirrhotics with ascites, and 25% in stable patients with cirrhosis, respectively [18, 19]. Besides, hypotonic hyponatremia associated with increased extracellular volume is the most frequent sort of hyponatremia observed in this population [19–21]. The risk of mortality in cirrhotics on transplant waiting list increases by 12% for each unit of sodium decrease between 120 and 135 mmol/L [18]. Cirrhotic patients with hyponatremia have higher 3-month mortality compared to those with normal serum sodium levels [18]. Because of that, as it was mentioned above, serum sodium variable was incorporated to prognostic MELD score [5–7]. In addition, hyponatremia is also associated with survival, falls, and cognitive dysfunction in the post-transplantation period [22, 23]. The

presence of hypotonic hyponatremia is relevant in cirrhotic patients since hyponatremia, like hyperammonemia and mild inflammation, has been documented to be significant factors involved in the pathogenesis of hepatic encephalopathy [24, 25]. It has been suggested that hepatic encephalopathy is related to astrocyte dysfunction secondary to intracellular glutamine accumulation due to hyperammonemia. Glutamine synthetase is an enzyme located into the astrocytes and is responsible for ammonia elimination through converting glutamate to glutamine. Since glutamine has osmotic properties, it can trigger intracellular edema with subsequent potential astrocyte damage, and functional alteration [18]. There are several conditions frequently observed in cirrhotics, such as diabetes mellitus, renal disease, hypokalemia, hypophosphatemia, hypoxia, and malnutrition, which are associated with high risk of osmotic demyelination induced by rapid correction of hyponatremia. Thus, the assessment of the underlying mechanism of hyponatremia and the presence of osmotic demyelination risk factors are crucial for the proper management of this entity [22]. According to the concept of the "*sick cell syndrome*," the presence of membrane transport failure, cellular sodium gain, and potassium loss can induce hyponatremia in severely ill patients. However, findings of normal or low erythrocyte sodium contents provide evidence against this mechanism for explaining hyponatremia in terminal cirrhotic patients [26]. Cirrhotic patients with ascites often have hyponatremia in the terminal stage of the disease, when serum sodium may be below 120 mmol/L, secondary to water retention due to a reduced delivery of sodium to the diluting segment (thick ascending limb of loop of Henle), as well as, an increased water reabsorption in the collecting tubules induced by vasopressin release [26]. The latter is the reason why V2-receptor antagonists (e.g., tolvaptan) have been proposed to treat hyponatremic cirrhotic patients [16–18]. However, in a recent study, Pose et al. evaluated the effect of tolvaptan on serum sodium in 9 patients with cirrhosis and severe hypervolemic hyponatremia (<125 mmol/L), and they found that only 2 out of the 9 patients (22%) gained an increase in serum sodium above 130 mmol/L that persisted throughout treatment. In the remaining patients, serum sodium either did not change or increased during the first days but decreased thereafter despite continuation of treatment. Thus, it seems that tolvaptan efficacy in severe hyponatremic cirrhotic patients is very limited [27–29]. It is also worth mentioning that hypotonic hyponatremia is frequently observed during hepatorenal syndrome. This syndrome is caused by an intense renal vasoconstriction secondary to marked splanchnic arterial vasodilation and reduction of effective arterial blood volume with subsequent activation of vasoconstrictor systems, such as renin–aldosterone axis and antidiuretic hormone. Hepatorenal syndrome is characterized by progressive renal failure, usually triggered by gastrointestinal hemorrhage, bacterial infections, or surgical procedures, and often associated with marked oliguria and profound hyponatremia [27]. In regard to hypotonic hyponatremia induced by endocrinologic alterations, low serum sodium can be related to hypothyroidism or adrenal insufficiency secondary to an autoimmune mechanism affecting the endocrinal glands and the liver (autoimmune hepatitis). It is worth mentioning that the coexistence of a polyendocrine deficiency disorder (Schmidt's syndrome) should be always ruled out since in this case the steroid replacement has to be prescribed before thyroxine therapy in order to avoid precipitating an addisonian crisis [23]. Regarding hyponatremia due to reset osmostat syndrome, it occurs when the threshold for vasopressin secretion is reset downward. These patients have normal water load excretion and intact urine-diluting ability after an oral water loading test. This condition is chronic and stable, and it can be caused by pregnancy, quadriplegia, malignancy, malnutrition, chronic debilitating disease, and chronic alcoholism [23, 30, 31]. In alcoholic patients, hyponatremia has a prevalence of 17%, and it can be induced by several mechanisms, such as: pseudohyponatremia secondary to alcohol-induced hypertriglyceridemia, reset osmostat, true volume depletion mainly due to gastrointestinal fluid losses, "*beer drinkers potomania,*" syndrome of inadequate antidiuretic hormone secretion (SIADH), and cerebral sodium wasting syndrome (CSW) due to alcohol-induced cerebral atrophy and dementia [31]. The "*beer drinkers potomania*" syndrome results from an excessive intake of very hypotonic fluid (beer) associated with a reduced free water excretion capability secondary to a reduced excretion of urinary solutes (low protein diet) [31]. As it was described above, hyponatremia can be induced by different mechanisms, and fractional excretion of uric acid (FEUA) can be useful for distinguishing them since FEUA value is usually low in hypovolemic states: volume depletion and edematous states (FEUA: <4%), normal in reset osmostat (FEUA: 4–11%), and high in syndrome of inadequate antidiuretic hormone secretion (SIADH) and CSW (FEUA > 11%). Regarding how to distinguish between SIADH and CSW, after serum sodium normalization FEUA value turns lower than 11% while remains higher than 11% in CSW [30]. Finally, other frequent causes of hypotonic hyponatremia in cirrhotic patients are: heart failure (cardiomyopathy secondary to alcohol or hemochromatosis), renal failure or nephrotic syndrome (glomerulonephritis, etc.), diarrhea (lactulose, infectious, etc.), pharmacological (terlipressin, loop diuretics, spironolactone, etc.), SIADH (interferon, lung and central nervous system infections, etc.) [22]. Pseudohyponatremia can also be found in cirrhotic patients, and it should be distinguished from real hyponatremia. There are two mechanisms of pseudohyponatremia depending on the

plasma tonicity. Regarding normotonic pseudohyponatremia, it is induced by an increased percentage of large molecular particles (lipids or proteins) in plasma (normotonic hyponatremia), since these large molecules do not contribute to plasma osmolality but do occupy volume in total plasma, but with the plasma osmolality remaining normal [23]. This spurious form of hyponatremia is not observed when direct ion-selective electrodes are used to determine electrolyte composition of plasma water. This pseudohyponatremia can be caused by severe dyslipidemia (interferon, nephrotic syndrome), marked hypergammaglobulinemia (interferon, autoimmune diseases), and/or intravenous immunoglobulin administration (liver transplant) [22]. In regard to hypertonic pseudohypernatremia, it is secondary to a shift of electrolyte-free water from the intracellular space into the intravascular compartment induced by the osmotic force of hyperglycemia. In this setting, the real serum sodium value (if no added glucose) can be estimated by adding 1.6 mmol/L to measured serum sodium for every 100 mg/dL increase above normal value of serum glucose. This phenomenon is frequently observed since diabetes mellitus is a risk factor for developing hepatopathy (non-alcoholic steato-hepatosis, diabetic hepatopathy), and the incidence of diabetes mellitus is high in patients suffering from cirrhosis (hepatogenous diabetes). Among its main causative agents are alcohol, hepatitis C,hemochromatosis, medication (glucocorticoids, interferon, tacrolimus, octreotide), and/or intercurrent diseases (hyperglycemia induced by sepsis) [22].

Hypernatremia

Even though severe hypernatremia (>150 mmol/L) shows low prevalence in cirrhotics (0.4%), moderate hypernatremia (>145 mmol/L) has been reported in up to 4% of these patients. Patients at risk of hypernatremia include those with reduced water intake (altered mental status, immobility, etc.) or increased water loss (diarrhea, diuretics, vaptans, etc.). High serum sodium is much more poorly tolerated (encephalopathy) than hyponatremia in cirrhotics, requiring urgent management. Since hypernatremia represents a free water deficit, it can be corrected by free water replacement [18] It is worth pointing out that normal serum sodium concentration in patients suffering from liver cirrhosis with severe hyperproteinemia or hyperlipidemia should raise the suspicion that true hypernatremia may be present (pseudonormonatremia).

Dyskalemias: hypokalemia and hyperkalemia

The serum potassium concentration can vary widely in unstable cirrhotic patients, with a higher prevalence of hypokalemia (20%) than hyperkalemia (12%) in this group [32].

Hypokalemia

Regarding hypokalemia, there are low body potassium stores in cirrhotic patients (sarcopenia) which predispose them to present low serum potassium level particularly in the context of malnutrition, secondary hyperaldosteronism, enteric potassium losses (diarrhea), magnesium depletion, renal tubular acidosis, or loop diuretics [1, 13, 19, 32, 33]. However, the increased sympathetic nervous activity is one of the most important factors in the pathogenesis of hypokalemia in cirrhotic patients, due to intracellular potassium shift induced by epinephrine. This sympathetic overactivity can be induced not only by the cirrhosis itself but also by acute hemorrhage or withdrawal syndrome in alcoholic cirrhotic patients [15]. Other causes of hypokalemia secondary to intracellular potassium shift in cirrhotics are: alkalemia, megaloblastic anemia treatment, and refeeding syndrome [33]. It is worth mentioning that terlipressin, which is usually used to treat bleeding esophageal varices and to improve renal function in hepatorenal syndrome, can induce hypokalemia by different mechanisms. Firstly, terlipressin induces marked arterial vasoconstriction, the amelioration of systemic hemodynamics suppresses the activity of vasoconstrictor systems, which in turn improves GFR leading to an increased potassium excretion [27]. Secondly, terlipressin is slowly transformed to lysine vasopressin which stimulates tubular potassium urinary excretion. Additionally, vasopressin can potentiate the stimulatory effect of aldosterone on potassium secretion in the collecting tubules [27, 33]. Because of the above-mentioned reasons, terlipressin can be used for treating hyperkalemia associated with hepatorenal syndrome, in order to try to avoid dialysis [27]. Hypokalemia can induce stupor and metabolic coma, since it is the extracellular potassium concentration which controls the renal ammonia production in cirrhotics. [34, 35]. The mechanisms by which hypokalemia, like metabolic acidosis, enhances production of ammonia is by lowering the intracellular pH of proximal tubule cells [35, 36]. A mild (200 mmol), short-term (5 days) potassium depletion is sufficient to stimulate renal amoniogenesis [36].

Hyperkalemia

Regarding hyperkalemia, it has been demonstrated that there is a reduced tolerance to exogenous potassium loading in cirrhotic patients. During the first three to 6 h after an acute potassium load, the bulk of potassium shifts normally into the intracellular space. Liver and muscles are the main buffering system in the distribution of potassium between

compartments partially mediated by insulin. However, a higher increase in serum potassium has been documented after an oral potassium load in cirrhotic patients when compared with healthy people despite similar urine excretion and despite an increase in the insulin secretion response in this population. Skeletal muscles mass reduction and decreased hepatic potassium uptake could be involved in the altered capacity of handling potassium loading in cirrhotic patients. Additionally, liver dysfunction contributes to decreased hepatic cellular potassium uptake despite the presence of insulin hypersecretion. Since insulin stimulates potassium uptake by cells through its action on sodium–potassium–ATPase pump, and also on sodium–hydrogen exchange across the cell membrane, the presence of a sort of insulin resistance has been postulated in order to explain this intolerance to potassium load in this population. Insulin level in cirrhotic patients has been largely reported higher than in normal subjects. Reduced hepatic insulin extraction and enhanced insulin secretion, due to a reduced negative feedback inhibition by circulating insulin, have been documented in cirrhotics. However, considering this, the cellular pathways involved in the mechanism of "resistance" to the effect of insulin on potassium transport and its possible link to resistance on glucose metabolism have not been determined yet [32, 37]. Patients with advanced cirrhosis are often treated with sparing potassium agents, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and beta-blockers. Special care should be taken with the intake of certain foods high in potassium (K+), such as orange (K+: 344 mg), banana (K+: 275 mg), or ginger (K+: 1343 mg), since they can trigger hyperkalemia [19, 38]. Cirrhotic patients sometimes require using simultaneously drugs which have antagonic effect on renal potassium handling, as is the case of furosemide and spironolactone. However, it has already been documented that in this pharmacological context there is a net increase in urinary potassium excretion, and this phenomenon can only be detected through transtubular potassium gradient index [37]. Serum potassium levels correlate directly with serum creatinine and urea and inversely with serum sodium in cirrhotics. The model incorporating serum potassium (K" model) can predict death in advanced cirrhotics with an excellent accuracy [19]. It has been documented in patients with cirrhotic ascites that serum potassium >4.8 mmol/L was associated with mortality within a year of hospitalization [38]. The MELD score reflects the underlying liver and renal function, and it is a validated predictor of survival in patients with liver diseases. It incorporates three widely available laboratory measurements, including the international normalized ratio (INR), serum creatinine, and bilirubin levels [39]. It showed a stronger predictive performance for high serum potassium than either serum creatinine or estimated glomerular filtration rate alone. Additionally, the MELD score showed good predictive performance for ARB-related hyperkalemia among hospitalized patients [39]. Hyperkalemia secondary to mineralocorticoid antagonists is more frequent in cardiac failure patients than in cirrhotic patients, except for those who are on nonspecific beta-blockers (e.g., propanolol) for treating portal hypertension [16]. Since ARBs are mainly eliminated via the hepatic and renal pathways, then lower doses are needed to achieve the same pharmacodynamic effects and to avoid hyperkalemia. However, the pharmacokinetics of irbesartan has been shown to be unaltered in patients with renal impairment or cirrhosis [39]. MELD score has shown to be useful in predicting hyperkalemia secondary to ARBs, so a high MELD score may indicate decreased elimination of ARBs from serum, and to have precaution in ARBs dose prescription [39–41]. Hyperkalemia in cirrhotic patients can also be induced by renal failure (e.g., hepatorenal syndrome), adrenal insufficiency, acidemia, hyperglycemia, and high-grade cytolysis (e.g., hemolysis, rhabdomyolysis) [42].

Acid–base disturbances

Acid–base imbalance generates different sort of internal milieu disorders such as acidosis, alkalosis, or their combination (double or triple acid–base disorders). Acidosis consists of a primary acid gain or a primary alkali loss, while acidemia indicates an increased serum H+ concentration (blood pH < 7.36). Conversely, alkalosis consists of a primary acid loss or primary alkali gain, and alkalemia indicates a decreased serum H+ concentration (blood pH > 7.44). Additionally, acidosis is classified in respiratory acidosis (carbon dioxide retention), normochloremic or high anion gap (AG) metabolic acidosis (bicarbonate conversion), and hyperchloremic or normal AG metabolic acidosis (bicarbonate loss). AG can be calculated by applying the following equation: AG = serum sodium-(serum chloride + serum bicarbonate), being its normal value 12 ± 4 mmol/L. Regarding alkalosis, it is usually classified in respiratory alkalosis (carbon dioxide high excretion) and metabolic alkalosis (bicarbonate gain) [43].

Respiratory alkalosis

Acid–base disorders are usually observed particularly in unstable cirrhotic patients, being chronic respiratory alkalosis (RA) the most prevalent acid–base alteration (64%), and it usually progresses from Child class A to class C ([32, 43]. Cirrhotic hyperventilation in stable cirrhosis can be induced by chronic hypoxemia (lung arteriovenous shunt), respiratory stimulating endogenous toxins (liver

arteriovenous shunt), respiratory center stimulation due to higher progesterone serum levels (reduced progesterone metabolism), and/or brain stem intracellular acidosis, since ammonia readily crosses the blood–brain barrier) [2, 32]. Additionally, hypocapnic (respiratory) alkalosis can induce hypokalemia by increasing renal potassium excretion and intracellular potassium shift, and hypophosphatemia by inducing phosphorus intracellular shift in this population [1, 2].

Metabolic alkalosis

Metabolic alkalosis is frequently found in cirrhotic patients mainly induced by secondary hyperaldosteronism (effective hypovolemia, loop diuretics, vomiting, glucocorticoid administration, etc.) high antiacid intake, and negative potassium balance [25, 29, 44]. In regard to diuretics, which are commonly used for the mobilization of ascites in unstable liver cirrhosis [1, 11], they can often induce not only metabolic alkalosis but also hypokalemia (loop diuretics and thiazides), hyperkalemia and metabolic acidosis (potassium sparing agents), and hyponatremia (all diuretics), depending on the sort of diuretic used and the patient's electrolyte balance [9]. The role of urea synthesis is not exclusively the elimination of potentially toxic ammonia, but also represents an important bicarbonate-consuming process, because urea synthesis is an energy-driven neutralization reaction of the bicarbonate base by the weak acid ammonium, or in chemical terms: 2 ammonium + 2 bicarbonate → urea + carbon dioxide + 3 water. Thus, the liver and the kidney work together to maintain ammonium and bicarbonate homeostasis. High serum bicarbonate levels and metabolic alkalosis in liver disease can be the consequence of an impaired bicarbonate-consuming urea synthesis due to a severe urea cycle dysfunction. In this context, an increased renal ammoniagenesis can help to maintain ammonium homeostasis when hepatic ammonium detoxication via the urea cycle fails. Additionally, elevated plasma glutamine levels, resulting from an impairment of urea synthesis, could be one of the signals to stimulate renal ammoniagenesis [29].

Metabolic acidosis

Metabolic acidosis with a high anion gap has been documented in around 10–20% of the cirrhotic patients, the most frequent causes are: lactic acidosis (sepsis or shock), alcoholic ketosis, and exogenous toxic acidosis (methanol or ethylene glycol ingestion) [32]. A slight defect was also documented in tubular acidification capability in many cirrhotic patients, but only a manifest renal tubular acidosis (RTA) in 1–10% of them. Metabolic acidosis with *normal anion gap* (hyperchloremic) is mainly secondary to distal RTA (type 1) secondary to systemic autoimmune illnesses, phosphorus deficit (malnutrition), or primary urinary acidification defect in cirrhotics. Besides, there are particular entities (e.g., Wilson disease, amyloidosis, etc.) which can induce simultaneously hepatic disease, and proximal RTA [2, 32]. Regarding distal RTA in cirrhotics, urinary sodium excretion can influence urinary acidity, since the sodium delivery to the distal tubules contributes to increase in their proton secretion capability. Consequently, increased sodium reabsorption at the proximal tubule and thick ascending limb of loop of Henle can impair distal proton secretion (voltage-distal RTA). Additionally, increased chloride reabsorption at thick ascending limb of loop of Henle (chloride shunt) can be another mechanism of distal RTA in this group [2]. This inability to lower urinary pH diminishes ammonia trapping in the urine and consequently leads to an increase in circulating ammonia and to aggravate the hepatic encephalopathy [1, 32, 44–46]. Hyperchloremic metabolic acidosis can also be induced by spironolactone (aldosterone antagonist) usually used in these patients in order to treat their edema due to secondary hyperaldosteronism [1]. The effect of spironolactone in lowering serum bicarbonate levels is secondary to aldosterone antagonism, which reduces hydrogen secretion (tubular acidosis secondary to antialdosteronism) and potassium secretion (reduced amoniogenesis secondary to hyperkalemia) [1].

Disorders of divalent ions and trace elements

Low serum calcium, phosphorus, and magnesium are the most frequent divalent ion alterations usually observed among cirrhotic patients [32]. Major disturbances also occur in vitamin D metabolism in cirrhotic patients. Even though the mammalian liver contains only trace quantities of vitamin D, this organ is crucial in vitamin D metabolism, since normal secretion of bile and its overall role in fat absorption is crucial in the absorption of exogenous vitamin D from the diet. Besides, the liver participates in the conversion of cholecalciferol (and ergocalciferol) to its biologically active form 25 hydroxycholecalciferol (25-OHD) via hydroxylation enzymes. Thus, hypocalcemia and metabolic bone disease are expected in cirrhotic patients. Low serum 25-OHD concentrations have been reported in patients with a variety of hepatic disorders, associated with calcium homeostasis disturbances and osteodystrophy such as osteomalacia, and secondary hyperparathyroidism [47]. The mechanisms for the low circulating serum 25-OHD concentrations in patients with chronic liver disease are multifactorial, such as the lack of vitamin D substrate due

to malnutrition, low sunlight exposure, malabsorption (bile acids lack), reduced hepatic 25-hydroxylation and vitamin D binding globulin synthesis. It is also possible that jaundice may interfere with the skin absorption of ultraviolet light. Since bilirubin absorbs light at the wavelength of 280 nm, which is also that required for the conversion of 7-dehydrocholesterol to pre-vitamin D3, interference in the cutaneous synthesis of cholecalciferol by bilirubin may be of importance in jaundiced cirrhotic patients [47]. Hypocalcemia is defined as an abnormal decrease in serum ionized calcium concentration, associated or not with low serum total calcium concentration. Low serum albumin and critical illness result in low total calcemia, but normal serum ionized calcium levels, and therefore do not cause symptoms of hypocalcemia. Hypocalcemia in cirrhotic patients can be secondary to malnutrition, malabsorption (obstructive jaundice or concomitant pancreatitis), vitamin D deficiency, loop diuretics, hypomagnesemia (urine calcium loss), coexistent renal disease, respiratory alkalosis, cinacalcet treatment (reduced cinacalcet metabolism), multiple infusions with citrated blood products, hypoparathyroidism, or paraneoplastic calcitonin (hepatic carcinoma) [32, 48, 49]. Regarding blood transfusions, exogenous citrate, a preservative used in banked blood products, is the main cause of hypocalcemia following blood transfusion, since citrate chelates with calcium to form a calcium–citrate complex which is finally metabolized in the liver. In this context, it has been documented that a rapid blood transfusion can cause more severe and prolonged ionized hypocalcemia in patients with liver dysfunction than in those with normal liver function, due to its impaired citrate metabolism [47]. It is worth mentioning that there is a particular cause of pseudohypocalcemia in cirrhotic patients. The use of gadolinium chelates as contrast agents increases the sensitivity and specificity of hepatic magnetic resonance imaging for diagnosing hepatocellular carcinoma in chronic hepatic patients. This contrast competitively inhibits the reaction between calcium ions and the dye complex, yielding a low-intensity color reaction that correlates with a falsely low serum total calcium level (within 24 h of undergoing the study). Since gadolinium is cleared by glomerular filtration and impaired renal function prolongs the clearance of this agent, patients with renal failure may be more likely to develop pseudohypocalcemia [48]. Parathyroid hormone seems to have a direct effect on the kidneys preventing sodium reabsorption in the proximal tubules, opposing the angiotensin II effect. Additionally, parathyroid hormone can counter-regulate an increased blood pressure by its vasodilator effects, while it can also stimulate renin and aldosterone release. However, sluggishness of this supplementary regulatory mechanism may occur in edematous status, as is the case of liver cirrhosis [49]. Besides, there is a feedback mechanism between the hormones responsible for sodium homeostasis and parathyroid hormone, which is relevant in this population and consists of the fact that angiotensin II stimulates and atrial natriuretic peptide inhibits parathyroid hormone release [50].

Magnesium metabolism

Since serum magnesium represents less than 1% of the total body magnesium content, the most reliable method to evaluate magnesium status is the magnesium loading test. This test consists of performing initially a magnesium sulfate infusion and later to determinate the urine excretion of magnesium over 24 h. In magnesium depletion, its uptake is increased (20–50%), while it is about 6% in normal magnesium status. When magnesium loading test was performed in cirrhotic patients, they showed an increased uptake of 34 ± 26%, which means the presence of a magnesium depletion status in this group [51]. Low serum and muscular magnesium content have been documented in alcoholic cirrhotic patients due to low magnesium intake (malnutrition), high intestinal magnesium losses (diarrhea, long-term use of proton pump inhibitors, renal magnesium losses (high serum alcohol level, hypophosphatemia, loop diuretics), intracellular shift induced by respiratory alkalosis [32, 52–55]. Patients suffering from alcoholic cirrhosis showed significantly reduced muscle strength, but when they are on spironolactone, muscle weakness is less pronounced, possibly because of the action of this drug on muscle magnesium and potassium content [54].

Phosphorus metabolism

Low serum phosphorus can be observed in cirrhotic patients due to different mechanisms, such as low phosphorus income (malnutrition, malabsorption), high phosphorus loss (tubulopathy), and intracellular phosphorus redistribution (respiratory alkalosis and refeeding syndrome) [25, 55]. Conversely, hyperphosphatemia, like hypermagnesemia, can be mainly documented in cirrhotic patients suffering from severe renal failure, and/or high cell destruction (rabdomiolysis, etc.) [32].

Trace elements

Finally, Nangliya et al. studied the trace elements (copper, zinc, and selenium) serum levels in one hundred fifty cirrhotic individuals of different sex (male–female), ages (young–old), and severity of hepatic disease (Child–Pugh A to Child–Pugh C). Serum level of copper was found significantly increased in patients with liver cirrhosis as compared

to healthy group, while serum zinc and selenium levels were significantly decreased in cirrhotic subjects as compared to normal controls. They also compared serum trace elements levels with severity of liver cirrhosis, and serum zinc, magnesium, and selenium levels were significantly decreased with advancement of liver disease as compared to early stage of cirrhosis and showed a significant negative correlation with Child–Pugh Score [56, 57].

Conclusions

Cirrhotic patients are predisposed to different water, electrolytes, acid–base and trace elements disorders since their homeostatic capability is undermined by the combination of their pathophysiological changes and the concomitant clinical conditions usually suffered by them.

Author contributions Musso CG and Juarez R collected the data and wrote the paper; Glassock RJ reviewed and edited the paper.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest for this article.

References

1. Gabow PA, Moore S, Schrier RW (1979) Spironolactone-induced hyperchloremic acidosis in cirrhosis. Ann Intern Med 90(3):338–340
2. Agarwal R, Knochel J (1996) Fluid and electrolyte disorders associated with alcoholism and liver disease. In: Kokko J, Tannen R (eds) Fluids and electrolytes. Saunders, Philadelphia, pp 449–485
3. Papper S (1976) Fluid and electrolyte disturbances in cirrhosis. Am J Med Sci 272(1):53–56
4. Guevara M, Cárdenas A, Uríz J, Gines P (2005) Prognosis of patients with cirrhosis and ascites. In: Gines P, Arroyo V, Rodés J, Schrier RW (eds) Ascites and renal dysfunction in liver diseases. Pathogenesis, diagnosis and treatment. Blackwell, Oxford, pp 260–270
5. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G (2006) Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 130(6):1652–1660
6. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA (2004) Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 40(4):802–810
7. Vaa BE, Asrani SK, Dunn W, Kamath PS, Shah VH (2011) Influence of serum sodium on MELD-based survival prediction in alcoholic hepatitis. Mayo Clin Proc 86(1):37–42
8. Chiandussi L, Bartoli E, Arras S (1978) Reabsorption of sodium in the proximal renal tubule in cirrhosis of the liver. Gut 19(6):497–503
9. Gentilini P, Laffi G, La Villa G, Raggi VC (1999) Pathogenetic factors and clinical elements in ascites and hepatorenal syndrome during liver cirrhosis. Ann Ital Med Int 14(4):264–284
10. Peña JC (1995) Renal and extra-renal mechanisms of sodium and water retention in cirrhosis with ascites. Rev Investig Clin 47(1):63–79
11. Caregaro L, Angeli P, Merlo A, Menon F, Rondana M, Merkel C, Gatta A (1987) Tubular handling of sodium and phosphate in non-ascitic liver cirrhosis. Scand J Clin Lab Investig 47(3):247–251
12. Kashani A, Landaverde C, Medici V, Rossaro L (2008) Fluid retention in cirrhosis: pathophysiology and management. QJM 101(2):71–85
13. Knauf H, Wenk E, Schölmerich J, Goerg KJ, Gerok W, Leser HG, Mutschler E (1990) Prediction of diuretic mobilization of cirrhotic ascites by pretreatment fractional sodium excretion. Klin Wochenschr 68(11):545–551
14. Knauf H, Mutschler E (1994) Liver cirrhosis with ascites: pathogenesis of resistance to diuretics and long-term efficacy and safety of torasemide. Cardiology 84(Suppl 2):87–98
15. Marchi S, Cecchin E (1988) Acute metabolic alkalosis with hypokalemia and azotemia following massive upper gastrointestinal hemorrhage in a 54-year-old alcoholic man with cirrhosis. Am J Nephrol 8:433–434
16. Schrier RW (2011) Use of diuretics in heart failure and cirrhosis. Semin Nephrol 31(6):503–512
17. Torre Delgadillo A (2005) Refractory ascites and dilutional hyponatremia: current treatment and new aquaretics. Rev Gastroenterol Mex 70(3):299–310
18. Lizaola B, Bonder A, Tapper EB, Mendez-Bocanegra A (2016) Cardenas A The changing role of sodium management in cirrhosis. Curr Treat Options Gastroenterol 14(2):274–284
19. Maiwall R, Kumar S, Sharma MK, Wani Z, Ozukum M, Sarin SK (2016) Prevalence and prognostic significance of hyperkalemia in hospitalized patients with cirrhosis. J Gastroenterol Hepatol 31(5):988–994
20. John S, Thuluvath PJ (2015) Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol 21(11):3197–3205
21. Arroyo V, Jiménez W (2000) Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. J Hepatol 32(1 Suppl):157–170
22. Liamis G, Filippatos TD, Liontos A, Elisaf MS (2016) Hyponatremia in patients with liver diseases: not just a cirrhosis-induced hemodynamic compromise. Hepatol Int 10(5):762–772
23. Goh KP (2016) Management of hyponatremia. Am J Med Sci 352(4):385–390
24. Iwasa M, Sugimoto R, Mifuji-Moroka R, Hara N, Yoshikawa K, Tanaka H, Eguchi A, Yamamoto N, Sugimoto K, Kobayashi Y, Hasegawa H, Takei Y (2016) Factors contributing to the development of overt encephalopathy in liver cirrhosis patients. Metab Brain Dis 31(5):1151–1156
25. Córdoba J, García-Martinez R, Simón-Talero M (2010) Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. Metab Brain Dis 25(1):73–80
26. Astrup J, Prytz H, Thomsen AC, Westrup M (1980) Red cell sodium and potassium contents in liver cirrhosis. Gastroenterology 78(3):530–534
27. Kalambokis G, Milionis H, Elisaf M, Tsianos EV (2005) Terlipressin avoids hemodialysis in the treatment of refractory hyperkalemia associated with renal dysfunction in cirrhosis. Am J Med 118(9):1051–1052

28. Pose E, Solà E, Piano S, Gola E, Graupera I, Guevara M, Cárdenas A, Angeli P, Ginès P (2016) Limited Efficacy of tolvaptan in patients with cirrhosis and severe hyponatremia. Real life experience. Am J Med S0002–9343(16):31017–31018
29. Fukui H (2015) Do vasopressin V2 receptor antagonists benefit cirrhotics with refractory ascites? World J Gastroenterol 21(41):11584–11596
30. Liamis GL, Milionis HJ, Rizos EC, Siamopoulos KC, Elisaf MS (2000) Mechanisms of hyponatraemia in alcohol patients. Alcohol Alcohol 35(6):612–616
31. Imbriano LJ, Mattana J, Drakakis J, Maesaka JK (2016) identifying different causes of hyponatremia with fractional excretion of uric acid. Am J Med Sci 352(4):385–390
32. Decaux G, Soupart A, Cauchie P, Delwiche F (1988) Potassium homeostasis in liver cirrhosis. Arch Intern Med 148(3):547–548
33. Dillingham M, Anderson R (1991) Water, electrolytes, and acid base disturbances in hepatic disease. In: Maxwell M, Kleeman C, Narins R (eds) Clinical disorders of fluid and electrolyte. Panamericana, Buenos Aires, pp 763–777
34. Stéphan F, Paillard F (1998) Terlipressin-exacerbated hypokalaemia. Lancet 351(9111):1249–1250
35. Artz SA, Paes IC, Faloon WW (1966) Hypokalemia-induced hepatic coma in cirrhosis. Occurrence despite neomycin therapy. Gastroenterology 51(6):1046–1053
36. Tannen R (1996) Potassium disorders. In: Kokko J, Tannen R (eds) Fluids and electrolytes. Saunders, Philadelphia, pp 111–199
37. Musso CG, Casciato P, Gaite L, Vilas, Navarro M, Martinez B, Rivera H, Luxardo R, Algranati L, Gadano A (2011) Assessment of the tubular handling of potassium in cirrhotic patients treated with a combination of furosemide + spironolactone. Electron J Biomed 3:39–43
38. Rivero Fernández M, Moreira Vicente V, Ledo Rodríguez A, del Árbol Ruiz, Olmos L (2007) Severe hyperpotasemia in a cirrhotic patient in relation with ginger consume. Med Clin (Barc) 129(10):397–399
39. Wallerstedt S, Simrén M, Wahlin S, Lööf L, Hultcrantz R, Sjöberg K, Gertzén HS, Prytz H, Almer S, Odén A (2013) Moderate hyperkalemia in hospitalized patients with cirrhotic ascites indicates a poor prognosis. Scand Gastroenterol 48(3):358–365
40. Sheen SS, Park RW, Yoon D, Shin GT, Kim H, Park IW (2015) The Model for end-stage liver disease score is potentially a useful predictor of hyperkalemia occurrence among hospitalized angiotensin receptor blocker users. J Clin Pharm Ther 40(1):48–54
41. Radó JP, Marosi J, Takó J, Dévényi I (1968) Hyperkalemic intermittent paralysis associated with spironolactone in a patient with cardiac cirrhosis. Am Heart J 76(3):393–398
42. Abbas Z, Mumtaz K, Salam A, Jafri W (2003) Factors predicting hyperkalemia in patients with cirrhosis receiving spironolactone. J Coll Physicians Surg Pak 13(7):382–384
43. Bruno CM (2016) Acid-base disturbance in liver cirrhosis. Eur J Gastroenterol Hepatol 28(3):363
44. Better OS (1982) Acquired distal renal tubular acidosis in man. Klin Wochenschr 60:1215–1217
45. Shear L, Bonkowsky HL, Gabuzda GJ (1969) Renal tubular acidosis in cirrhosis. A determinant of susceptibility to recurrent hepatic precoma. N Engl J Med 280(1):1–7
46. Häussinger D, Steeb R, Gerok W (1990) Ammonium and bicarbonate homeostasis in chronic liver disease. Klin Wochenschr 68(3):175–182
47. Wills MR, Savory J (1984) Vitamin D metabolism and chronic liver disease. Ann Clin Lab Sci 14(3):189–197
48. Kefalas CH, Murray NG, Aguanno JJ, Dockery WD, Weinstein JS, Anderson K, Klintmalm GB (2004) Pseudohypocalcemia after magnetic resonance imaging with gadolinium in patients with cirrhosis. Liver Transpl 10(1):136–140
49. Akinci B, Comlekci A, Tankurt E (2009) Hypercalcemia of primary hyperparathyroidism was treated by cinacalcet in a patient with liver cirrhosis. Exp Clin Endocrinol Diabetes 117(3):142–145
50. Chung HS, Cho SJ, Park CS (2012) Effects of liver function on ionized hypocalcaemia following rapid blood transfusion. J Int Med Res 40(2):572–582
51. Jespersen B, Fogh-Andersen N, Brock A (1994) Parathyroid hormone in blood pressure and volume homeostasis in healthy subjects, hyperparathyroidism, liver cirrhosis and glomerulonephritis. A possible interaction with angiotensin II and atrial natriuretic peptide. Scand J Clin Lab Investig 54(7):531–541
52. Koivisto M, Valta P, Höckerstedt K, Lindgren L (2002) Magnesium depletion in chronic terminal liver cirrhosis. Clin Transpl 16(5):325–328
53. de la Coba Ortiz C, Argüelles Arias F, Martín de Argila de Prados C, Júdez Gutiérrez J, Linares Rodríguez A, Ortega Alonso A, Rodríguez de Santiago E, Rodríguez-Téllez M, Vera Mendoza MI, Aguilera Castro L, Álvarez Sánchez A, Andrade Bellido RJ, Bao Pérez F, Castro Fernández M, Giganto Tomé F (2016) Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Española de Patología Digestiva. Rev Esp Enferm Dig 108(4):207–224
54. Musso CG (2009) Magnesium metabolism in health and disease. Int Urol Nephrol 41(2):357–362
55. De Marchi S, Cecchin E, Basile A, Bertotti A, Nardini R, Bartoli E (1993) Renal tubular dysfunction in chronic alcohol abuse–effects of abstinence. N Engl J Med 329(26):1927–1934
56. Aagaard NK, Andersen H, Vilstrup H, Clausen T, Jakobsen J, Dørup I (2002) Muscle strength, Na, K-pumps, magnesium and potassium in patients with alcoholic liver cirrhosis—relation to spironolactone. J Intern Med 252(1):56–63
57. Nangliya V, Sharma A, Yadav D, Sunder S, Nijhawan S, Mishra S (2015) Study of trace elements in liver cirrhosis patients and their role in prognosis of disease. Biol Trace Elem Res 165(1):35–40