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ORIGINAL ARTICLE

Comparative study of spot urine Na/K ratio and 24-hour urine sodium in natriuresis evaluation of cirrhotic patients with ascites

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Abstract

Introduction: The ''spot'' urine sodium/potassium (Na/K_u) ratio is a convenient tool to identify sodium excretion < 78 mequiv./d. It has been established that this ratio is as useful and accurate as 24-h urine sodium (Na_{u24h}), but no Latin American study has evaluated this issue. The aim of this study is to evaluate the accuracy of the Na/K_u ratio and to compare it to Na_{u24h}.

Materials and methods: This cross-sectional study included 20 patients with decompensated liver cirrhosis and ascites.

Results: Mean age was 56.1 ± 11.8 years old, 70% were men and 60% presented Na_{u24h} < 78 mequiv./d. Poor sodium excretion group presented higher MELD score ($P = 0.002$), creatinine ($P = 0.029$), AST ($P = 0.027$) and bilirubin ($P = 0.013$) levels, and also lower median spot sodium urine ($P = 0.001$). There was a high positive correlation between Na/K_u ratio and Na_{u24h} ($r = 0.857$; $P < 0.001$) and negative correlation with MELD ($r = -0.498$; $P = 0.025$) and serum creatinine ($r = -0.498$; $P = 0.025$). The AUROC of Na/K_u in predicting Na_{u24h} < 78 mequiv./d was 0.948 ± 0.046 and the classical Na/K_u ratio cut-off (≤ 1.0) showed PPV = 70%, NPV = 90%, accuracy = 80%, sensitivity = 88% and specificity = 75%.

Conclusion: $Na/K_u \leq 1$ is sensitive and specific, and substantially correlates with Na_{u24h}, which enables the use of this test in the routine evaluation of patients with liver cirrhosis decompensated in ascites.

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Análise comparativa da razão Na/K em amostra isolada de urina com sódio na urina de 24 horas na avaliação da natriurese de cirróticos com ascite

Resumo

Introdução: A razão sódio/potássio em amostra isolada de urina (Na/K_u) é uma ferramenta apropriada para identificar a excreção urinária de sódio < 78mEq/d. Foi estabelecido que essa razão é tão útil e acurada quanto a dosagem de sódio na urina de 24 horas (Na_{u24h}), contudo nenhum estudo Latino Americano avaliou essa questão. O objetivo desse estudo foi avaliar a razão Na/K_u e compará-la a dosagem de Na_{u24h}.

Material e métodos: Estudo transversal que incluiu 20 pacientes com cirrose hepática descompensada em ascite.

Resultados: A idade média foi de 56,1 ± 11,8 anos, 70% eram homens e 60% apresentaram Na_{u24h} < 78 mEq/d. O grupo mau excretor de sódio apresentou maior escore MELD (P = 0,002), creatinina (P = 0,029), AST (P = 0,027), bilirrubinas (P = 0,013), e também menor mediana de sódio em amostra isolada de urina (P = 0.001). Houve correlação positiva entre razão Na/K_u e Na_{u24h} (r = 0,857; P < 0,001) e correlação negativa com MELD (r = 0,498; P = 0.025) e creatinina sérica (r = −0,498; P = 0,025). A AUROC da razão Na/K_u em predizer Na_{u24h} < 78 mEq/d foi de 0,948 ± 0,046 e o cut-off clássico da razão Na/K_u (≤1.0) exibiu VPP = 70%, VPN = 90%, acurácia = 80%, sensibilidade = 88% e especificidade = 75%.

Conclusão: Na/K_u ≤ 1 é sensível e específico e se correlaciona substancialmente com Na_{u24h}, o que permite o uso desse teste na avaliação rotineira de pacientes com cirrose descompensada em ascite.

Introduction

Ascites is defined as the pathological accumulation of fluid in the peritoneal cavity.[1] There are three theories to explain the development of ascites in individuals with liver cirrhosis: underfill, overflow and vasodilatation. The modern view suggests that the three states are in greater or lesser extent, present in the same patient with cirrhosis.[2] The underfill theory proposes that the two most important factors in the development of ascites are portal venous hypertension and failure of the liver to synthesize of albumin, which results in a reduction in plasma osmotic pressure. These factors lead to reduction in effective circulating volume, which activates the renin–angiotensin–aldosterone system and promotes the absorption of sodium and water. Ascites may be formed partly from the hepatic lymph and thoracic duct would be responsible for removing it. By these various compensatory mechanisms, body fluids are depleted, more ascites is formed and the cycle restarts.[3] The overflow theory states that, initially, there would be increased sodium retention by the kidneys which would increase the effective circulating volume. Peripheral vascular resistance would decrease to accommodate hypervolemia. The encounter between hypervolemia and increased portal pressure would result in overflow that would form the ascites.[4] The vasodilation theory explains that the ascites formation would start with arterial vasodilation in the splanchnic circulation secondary to portal hypertension. Then a hyperdynamic circulation would occur to maintain homeostasis. This compensatory mechanism, with the progress of the disease would be insufficient to support homeostasis. Blood pressure would decrease which would stimulate the baroreceptors and lead to increased homeostatic activity of the sympathetic

nervous system, the renin–angiotensin–aldosterone system, circulation levels of antidiuretic hormone, and retention of sodium and water. The activation of these systems associated with decreased lymphatic return by splanchnic congestion would form the ascites.[4] The vasodilation theory would be present in pre-ascitic phase and it would be important in any subsequent developments. The overflow theory would be the most important aetiology in the first months of the development of ascites in individuals with cirrhosis, and the underfill theory explains most of the findings of ascites in patients with chronic decompensation.[2]

Ascites is considered the most common of the three major complications of cirrhosis. Other complications are hepatic encephalopathy and oesophageal variceal bleeding. About 50% of patients with compensated cirrhosis develop ascites over 10 years of follow-up.[5] In 1 year with ascites, approximately 15% of patients will die, and 44% will die in 5 years.[6]

The mainstay treatments of patients with cirrhosis and ascites are: a low sodium diet (2000 mg/day = 88 mequiv./day) and diuretics.[7] The measurement of urinary sodium excretion has been used for many years to identify the patient under sodium restrictive diet and distinguish him from those who require diuretics. Although spot urine Na measurement could be useful in this setting, the sodium excretion is not uniform during the day, which complicates the interpretation of results. For that reason, the most used method to estimate natriuresis is the measurement of 24-h urine sodium excretion (Na_{u24h}). Patients with a restricted diet of 2000 mg of salt that does not lose weight and have Na_{u24h} excretion ≥78 mequiv. per day are usually labelled as noncompliant diet.[8] Although widely requested in evaluating this group of patients, the collection of Na_{u24h} can be cumbersome to the patient,

nursing and physician. The patient may have difficulty storing urinary content (e.g., hepatic encephalopathy, management of the collector, embarrassment in front of other patients and visitors). Nursing may present difficulty in monitoring the urine collection and checking whether the collected volume actually corresponds to 24-h urine. The physician, when requesting the test makes urges for the result, which usually exceeds the 24 h of collection.

The Na/K ratio in ''spot'' urine sample (Na/K_u) is a practical way to identify Na_{u24h} dosage lower than 78 mequiv.. Some evidence shows that this ratio is as useful and accurate as the collection Na_{u24h}, but no Latin American study has evaluated this issue.[9-15] This study aims to evaluate the accuracy of the Na/K_u ratio and compare it to Na_{u24h} in the evaluation of natriuresis in patients with decompensated liver cirrhosis ascites.

Methods

This cross-sectional study assessed individuals with decompensated liver cirrhosis and ascites admitted to the hospital or treated in the outpatient clinics of Gastroenterology at University Hospital Polydoro Ernani de São Thiago of Federal University of Santa Catarina. Between August 2010 and January 2012, 42 patients admitted in the gastroenterology ward or in the outpatient gastroenterology clinic. The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the local research ethics committee under number 322597.

Clinical variables of all individuals included in the study were collected in interview and confirmed in medical records. Laboratory parameters were extracted from medical records. The following variables were studied: age, gender, race, being a carrier of hepatitis B or C, alcohol consumption >40 g/day, diabetes mellitus, hypertension, liver cancer, history of upper gastrointestinal bleeding, spontaneous bacterial peritonitis, use of diuretics; serum creatinine, haemoglobin, platelets, serum sodium, serum potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), bilirubin, serum albumin, international normalized ratio (INR), activated prothrombin time (APT); Na_{u24h} dosage, sodium and potassium in urine sample. Biochemical liver tests AST, ALT, ALP and GGT were expressed as times the upper limit of normal (xULN). The other laboratory variables were expressed as absolute values. Examination of bilirubin, INR and creatinine values were used in the MELD calculation (Model for End-stage Liver Disease).[16] The Na/K_u ratio is calculated on the values of sodium and potassium in ''spot'' urine sample. Urine was collected within less than or equal to 48 h from admission. Collection of 24-h urine sample for calculation of sodium was done in sterile plastic containers by recording the volume in 24 h; starting at 8:00 a.m. Instructions were given to assure completeness of collection. All samples were processed on the day of collection. In order to obtain the whole 24-h urinary sodium, sodium concentration was multiplied by the volume in litres. Random urine samples were obtained before or after completion of 24-h collection for measurement of 'spot' Na/K ratio. Any kidney disease was excluded by medical history, urinalysis, serum creatinine and ultrasound examination of the kidneys.

Numerical variables were expressed as mean and standard deviation, whereas categorical variables were described in absolute numbers and proportions. Continuous variables were compared using either Student's t test or Mann–Whitney when appropriate, categorical variables were analysed using either Chi-squared test or Fisher's exact test. A P-value < 0.050 was considered statistically significant. The correlation between the Na_{u24h} and Na/K_u ratio was evaluated by the Spearman's correlation coefficient. Diagnostic accuracy of the Na/K_u ratio was analysed by estimating the area under the receiver operating characteristics curve (AUROC) and by calculating sensitivity, specificity, positive and negative predictive value. All tests were performed by the statistics software SPSS, version 17.0 (SPSS, Chicago, IL, USA).

Results

Sample analysis

Between August 2010 and January 2012, 42 patients admitted in the gastroenterology ward were evaluated for inclusion as they present liver cirrhosis decompensated in ascites. Twenty-two patients without urinary sodium dosage were excluded. Twenty patients with decompensated liver cirrhosis and ascites were included. Among them, 60% presented poor urinary sodium excretion (Na_{u24h} dosage lower than 78 mequiv.).

Among the 20 included individuals, the mean age, standard deviation and median were 56.1 ± 11.8 (54.5) years, 70.0% were men, 66.7% were Caucasian. Regard to the aetiology of cirrhosis: 33.3% had alcohol abuse and hepatitis C virus, 27.8% had alcohol only (Table 1). Three patients had hepatocellular carcinoma.

Evaluation of included patients according to the ability to excrete sodium (Na_{u24h})

When individuals with poor urinary sodium excretion were compared to those with $Na_{u24h} \geq 78$ mequiv. (Tables 1 and 2), they exhibited a higher proportion of male sex (91.7% vs. 37.5%; $P = 0.018$); higher mean MELD scores (16.3 ± 9.3 vs. 5.0 ± 3.5; $P = 0.002$), higher mean creatinine (1.1 ± 0.4 mg/dL vs. 0.8 ± 0.2 mg/dL; $P = 0.029$), higher AST means (3.1 ± 1.7 vs. xULN 1.6 ± 0.7; $P = 0.027$), higher median bilirubin (1.1 g/dL vs. 0.3 g/dL; $P = 0.013$) and lower median spot urine sodium (21.5 mequiv./L 222 vs. 137.0 mequiv./L; $P = 0.001$); $P =$ no. No differences were observed with respect to age, race, aetiology of cirrhosis, diabetes, hypertension, hepatocellular carcinoma, prior upper gastrointestinal bleeding, spontaneous bacterial peritonitis, current use of diuretics, urea, haemoglobin, platelets, serum sodium, serum potassium, spot urine potassium, ALT, ALP, GGT, albumin, and INR when individual with poor urinary sodium excretion were compared to those with $Na_{u24h} \geq 78$ mequiv.

There was a strong positive correlation between the Na/K_u and Na_{u24h} ($r = 0.857$, $P < 0.001$) (Fig. 1). A negative correlation between MELD score ($r = -0.498$; $P = 0.025$)

Table 1 Distribution of clinical variables from 20 individuals with liver cirrhosis decompensated in ascites.

Characteristics	All individuals $n = 20$
Age (years)[a]	56.1 ± 6.8
Male (%)	70.0
Caucasian (%)	66.7
Hepatitis B (%)[b]	22.2
Hepatitis C (%)[b]	44.4
Alcoholism (%)[b]	61.1
Diabetes mellitus (%)[c]	37.5
Hypertension (%)[c]	56.3
HCC (%)	15.0
History of upper GI bleeding (%)[c]	60.0
SBP present (%)[c]	13.3
Use of diuretics (%)[c]	28.6

HCC, hepatocellular carcinoma; GI, gastrointestinal; SBP, spontaneous bacterial peritonitis.
[a] Mean $\pm$ standard deviation.
[b] Available for 18 patients.
[c] Available for 16 patients.

and serum creatinine ($r = -0.498$; $P = 0.025$) was evidenced. There were no significant correlations between the Na/K$_u$ ratio and age, platelet count, serum sodium, AST, ALT, direct bilirubin, albumin and INR.

Performance of the Na/K$_u$ ratio in predicting 24 h urinary sodium excretion

The AUROC for Na/K$_u$ in the prediction of Na$_{u24h}$ < 78 mequiv. was 0.948 ± 0.046, $P = 0.001$ (Fig. 2). Table 3 shows in details
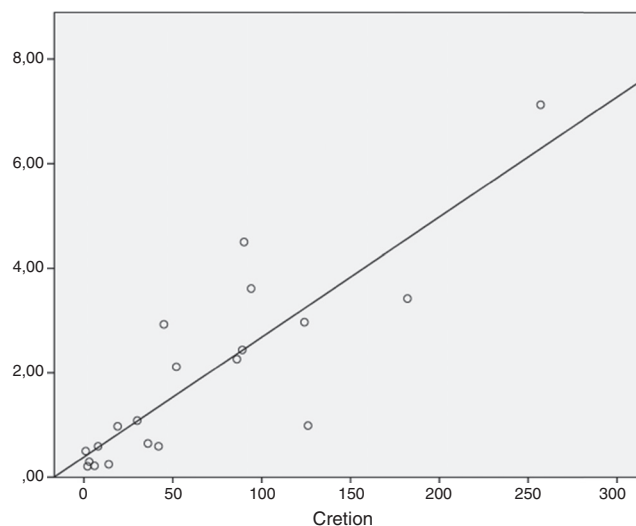

Figure 1 Scatter plot of Na/K urine sample ratio against 24 h urine sodium excretion ($r = 0.857$; $P < 0.001$).

the diagnostic performance of the Na/K$_u$ ratio in predicting Na$_{u24h}$ < 78 mequiv. For the Na/K$_u$ ratio, the classical cut-off (≤ 1.0) showed 70% positive predictive value (PPV) to diagnose Na$_{u24h}$ dosage < 78 mequiv. with negative predictive value (NPV) of 90%, accuracy of 80%, 88% sensitivity and specificity of 75%.

Discussion

Cirrhosis is the twelfth leading cause of death in the United States of America.[17] Several authors evaluated patients with decompensated liver cirrhosis ascites. Usually, the studied

Table 2 Distribution of laboratory variables from 20 individuals with liver cirrhosis decompensated in ascites according to the 24-h urine sodium excretion (Na$_{u24h}$).

Characteristics	All individuals $n = 20$	Na$_{u24h}$ < 78 mequiv. $n = 12$	Na$_{u24h} \geq 78$ mequiv. $n = 8$	P^c
Creatinine (mg/dL)[a]	1.0 ± 0.4	1.1 ± 0.4	0.8 ± 0.2	0.029
Urea (mg/dL)[b]	36.0	44.0	21.5	0.069
Haemoglobin (g/dL)[a]	10.7 ± 2.9	9.9 ± 2.7	12.0 ± 2.8	0.116
Platelets (/mm^3)[b]	83,500	83,500	82,000	0.787
Serum sodium (mequiv./L)[b]	137.5	137.0	138.0	0.811
Spot urine sodium (mequiv./L)[b]	37.5	21.5	137.0	0.001
Serum K (mequiv./L)[a]	4.2 ± 0.7	4.3 ± 0.9	4.1 ± 0.4	0.605
Spot urine K (mequiv./L)	34.6 ± 11.7	31.1 ± 10.7	39.8 ± 11.7	0.104
AST (xULN)[a]	2.5 ± 1.6	3.1 ± 1.7	1.6 ± 0.7	0.027
ALT (xULN)[a]	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.5	0.975
ALP (xULN)[b]	0.7	0.8	0.7	0.589
GGT (xULN)[b]	1.7	1.5	2.0	0.939
Direct bilirubin (mg/dL)[b]	0.8	1.1	0.3	0.013
Albumin (g/dL)[a]	2.6 ± 1.0	2.4 ± 1.0	3.0 ± 1.0	0.201
Prothrombin activity (%)[a]	55.3 ± 24.0	48.0 ± 25.0	66.3 ± 18.8	0.096
MELD[a]	11.8 ± 9.3	16.3 ± 9.3	5.0 ± 3.5	0.002

K, potassium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; xULN, times the upper limit of normal; MELD, model for end stage liver disease.
[a] Mean $\pm$ standard deviation.
[b] Median.
[c] Student's t test, Mann–Whitney or Fisher's exact test when appropriated.

Table 3 Diagnostic performance of spot urine sodium-to-potassium ratio (Na/K_u) ratio in predicting 24-h urine sodium excretion (Na_{u24h}) < 78 mequiv.

	Cut-off	Accuracy (%)	Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
Na/K_u	<1.0	80	88	75	70	90

PPV, positive predictive value; NPV, negative predictive value.

population is predominantly composed by men, 59--74%, age ranging from 53.6 to 60 years.[18--20] In this study it has been observed that 70% of subjects were male; mean age was 56.1 years, which coincides with that described in literature. With regard to the aetiology of cirrhosis, it varies according to the prevalence of the diseases on the studied area, with a higher prevalence of HBV (64.8%) in China, higher incidence of alcoholic cirrhosis (76.4%) in Germany (19) and Barcelona (44.7%).[18] The present study demonstrated a higher prevalence of HCV as compared to Europe and Asia, the latter being an area of high prevalence of HBV[21] and exhibits high prevalence of alcoholism as a cause of chronic liver disease.

In cirrhosis, the development of ascites and diuretic response are determined by the renin--angiotensin--aldosterone and renal sodium handling.[22] This study observed that patients presenting with more severe liver disease (MELD, creatinine, bilirubin, AST) are those who have lowest urinary sodium excretion. Likewise, Cholongitas et al. recently demonstrated that the factors independently associated with poor urinary sodium excretion in cirrhosis are albumin, creatinine and Na/K_u.[11]

The Na/K_u ratio emerged as an option to Na_{u24h} in evaluating the ability of cirrhotic patients with ascites to excrete salt. During ascites treatment, absence of weight loss may be secondary to poor response to diuretics or a consequence of non-adherence to low sodium diet. It is important to recognize these differences to avoid possible complications caused by unnecessary increase in dosage of a diuretic, such as hepatic encephalopathy, renal dysfunction and electrolyte disturbance, and complications caused by the drainage of large volumes of ascitic fluid by paracentesis as mechanical trauma and circulatory dysfunction.[23] Despite the good performance of the AUROC for Na/K_u in the prediction of Na_{u24h} < 78 mequiv., these data should be cautiously interpreted, as Na/K_u ration is non-linear. Nevertheless, respectable negative predictive value, accuracy, sensitivity and specificity were good enough to support its routine use. Furthermore, these findings are supported by previous studies. After extensive literature review it has been verified that only eight studies[9--15,24] compared Na/K_u ratio with Na_{u24h} dosage in order to identify poor urinary sodium excretion (Na_{u24h} < 78 mequiv.), and only three of them are complete articles.[13,14,24] Two studies are letters to the editor[11,15] and three are abstracts published in congress annals[9,10,12], one of which is unavailable for consultation.[9] These studies have identified different cut-offs for the Na/K_u ratio. The cut-off point of 1 currently recommended by American Association for the Study of Liver Diseases,[1] is the most sensitive and specific 64--95% and 75--92%.[10--12,15] However, Rojpalakorn et al. have identified low specificity (6%) for the classic cut-off, thus has questioned their practical application.[24] In the present study, besides the high sensitivity and specificity demonstrated for 1 cut off Na/K_u ratio, it has been found strong positive correlation between Na/K_u ratio and Na_{u24h}, previously demonstrated by Pinto-Marques et al.[15] Other cut-off points for the Na/K_u ratio have been studied. The cut-offs 1.25 and 2.5 have demonstrated a specificity and a sensitivity ranging from 72% to 88% and 85% to 96%, respectively.[13,14]

Stiehm et al. analysed 729 specimens of urine in 21 patients, a similar number of individuals included in this study.[10] The circadian variability was assessed analysing the Na/K_u ratio according to diuretic administration in different day periods and no differences were demonstrated between groups. Likewise, Park et al. analysed two dosages Na/K_u ratio, in the morning and afternoon to check whether the not uniform sodium excretion during the day interfere in the ratios inferred.[14] Apparently the urinary potassium excretion varies in accordance with sodium, maintaining the proportion at different times of day. The present study evaluated only a single urine sample from each patient, as previously published by El-Bokl et al. and Rojpalakorn et al.[13,24]

Based on these data, we conclude that the Na/K_u ratio cut off point of 1.0 may be sensitive and specific to assess the ability of sodium excretion in patients with liver cirrhosis and ascites and it correlates strongly with Na_{u24h} dosage, which enables the utilization of this simple and useful test in the routine evaluation of these patients.
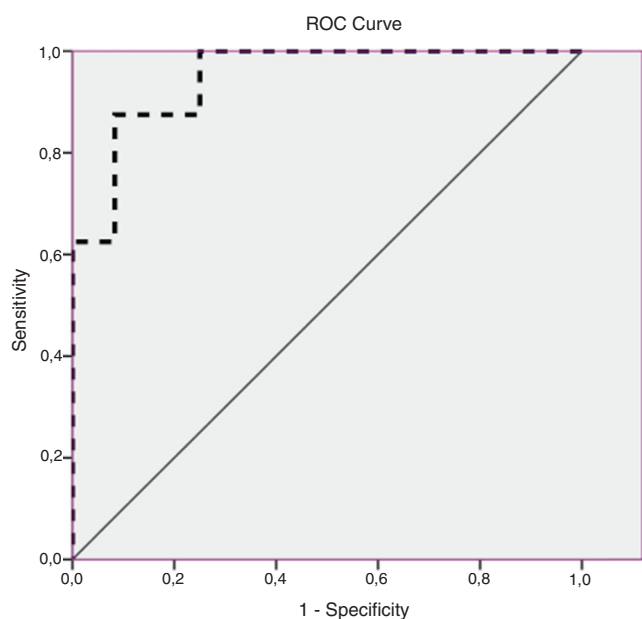
Figure 2 ROC curve of Na/K ratio in ''spot'' urine sample in predicting 24 h urine sodium excretion lower than 78 mequiv.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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