Sodium handling is associated with liver function impairment and renin-aldosterone axis activity in patients with preascitic cirrhosis without hyponatremia

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Abstract

Background In cirrhotic patients awaiting liver transplantation, serum sodium concentration is related to prognosis. However, abnormalities in sodium homeostasis are evident even in the early preascitic stage of cirrhosis. We aimed to investigate whether parameters of renal sodium handling (serum sodium, urinary sodium and fractional exertion of sodium (FeNa%) correlate with markers of liver function and renin-aldosterone axis activity in patients with preascitic cirrhosis without hyponatremia.

Methods Patients with preascitic cirrhosis without hyponatremia underwent routine blood and urine laboratory tests, including markers of liver function impairment and sodium homeostasis.

Results Thirty eight cirrhotic patients (22 men) with mean age of 57.3±12.2 (SD) years were included. Twenty six and twelve patients were at Child-Pugh stage A and B cirrhosis respectively. Eighteen patients had a Model for End-stage Liver Disease (MELD) score of ≤9 and twenty had MELD >9. Serum sodium was found to differ significantly between Child-Pugh stage A and B cirrhotics (mean 142.8±2.0 mmol/L vs. 140.5±3.3 mmol/L, p<0.05). Serum sodium was also found to differ significantly between patients with MELD score ≤9 and >9 (mean 143.3±2.0 mmol/L vs. 140.9±2.8 mmol/L, respectively, p<0.01). Serum sodium correlated negatively with the international normalized ratio (INR) (r=-0.51, p<0.01), aldosterone (r=-0.40, p<0.05), Child-Pugh and MELD scores (r=-0.34, p<0.05 and r=-0.45, p<0.05 respectively). FeNa% correlated negatively with renin and aldosterone (r=-0.56, p<0.001 and r=-0.50, p<0.01 respectively).

Conclusion Serum sodium concentration is a good surrogate marker of liver function impairment not only in late-stage liver cirrhosis before transplantation but also in the early preascitic stage.

Keywords cirrhosis, liver function markers, serum sodium, Child-Pugh stage, MELD score

Introduction

Sodium and water retention in cirrhotic patients is a well-recognized mechanism implicated in ascites formation. Moreover, sodium handling abnormality leading to sodium retention and weight gain in upright position has been described in preascitic cirrhosis and has been attributed to stimulation of the renin-angiotensin-aldosterone system (RAAS) [1].

Recent reports documented that dilutional hyponatremia provided prognostic information about mortality in patients with end-stage liver disease awaiting liver transplantation [2-6]. Spot urinary sodium is a useful marker of sodium retention in patients with decompensated cirrhosis, yet it is not regarded as a reliable test because of the lack of uniform excretion of sodium throughout the day [7]. A spot urine measurement of fractional excretion of sodium (FeNa%= [urinary sodium/serum sodium] x [serum creatinine/urinary creatinine]) is easy to calculate and does not depend on accurate-timed urine volume collection or sodium intake.

We hypothesized that abnormal sodium handling is pathogenetically related to the degree of liver dysfunction not only in cirrhotic patients with ascites but also in preascitic patients. We investigated whether parameters of renal sodium handling (serum sodium, urinary sodium and FeNa%) correlate...
with markers of liver impairment and RAAS activity in patients with less advanced liver disease.

Materials and Methods

Ambulatory adults with preascitic cirrhosis, irrespective of etiology, sex, or age, were included in this study. Patients with known history of arterial hypertension, treated or untreated, heart failure, hepatic encephalopathy, active infection or hemorrhage within the last 4 weeks before the study, active alcohol consumption or symptoms of withdrawal and with serum creatinine >132.6 μmol/L or bedridden, were excluded. No special instructions were given regarding salt intake. Diuretics, beta-blockers or other drugs affecting blood pressure, when used, were stopped 7 days before and during the study. No patient had serum Na <135 mmol/L or urinary Na <10 mmol/L. Participants were informed about the purpose and procedures of the study and gave written consent before they were enrolled. The study protocol was approved by the Hospital Scientific Committee.

Blood samples were taken for the International Normalized Ratio (INR), serum total bilirubin, albumin, sodium, renin and aldosterone. Model for End-stage Liver Disease (MELD) score [8,9] and Child-Pugh score were assessed. Morning blood samples were obtained after 8-12 h fasting and after the subjects had been awake and active for at least 1 h. Random spot urine samples were taken for sodium, creatinine and FeNa%. Participants were asked to discard the first morning urine, so that sodium concentration could be measured in urine produced in ambulatory conditions. All laboratory tests were performed by the means and facilities of the Hypertension Center, 3rd University Department of Medicine, Sotiria Hospital. Renin and aldosterone concentration was measured after serum specimens were centrifuged and frozen at below -20°C. Serum renin and aldosterone concentration was measured with Nichols Advantage® Direct Renin and Nichols Advantage® Aldosterone chemiluminescence methods (normal values in upright position 3.3-41 μIU/mL for renin and 3-34 ng/dL for aldosterone).

Statistical analysis

Logarithmic transformation was performed in not normally distributed data (total bilirubin, renin, aldosterone and FeNa%). Serum and urinary sodium concentrations and FeNa% were compared between patients of Child-Pugh stage A and B, as well as between patients with MELD score ≤9 and >9, using t-test. A p value below 0.05 was considered statistically significant. The associations between serum and urinary sodium, and total bilirubin, INR, albumin, renin, aldosterone, Child-Pugh score (points) and MELD score were assessed using Pearson correlation coefficients. Statistical software MINITAB INC Statistical Software (release 13.31) (State College, Pennsylvania, USA) was used.

Results

Thirty eight cirrhotic patients (22 men) with mean age 57.3±12.2 (range 31-81 years), were included in this study. The cause of cirrhosis was alcohol abuse, viral hepatitis and miscellaneous in 14, 17 and 7 patients respectively. Table 1 summarizes the main characteristics of the study participants. Twenty six and 12 patients were at Child-Pugh stage A and B respectively. Mean Child-Pugh score points were 6.1±1.4 in all patients, 5.3±0.4 in Child-Pugh A group and 7.7±1.1 in Child-Pugh B group. Mean MELD score was 10.6±3.2 (7-21) in all patients. Eighteen patients had MELD score ≤9 and 20 patients >9.

Serum sodium differed significantly between Child-Pugh stage A and B cirrhotics (mean 142.8 mmol/L vs. 140.5 mmol/L, p <0.05) (Table 1). FeNa% was 0.6 and 0.5 in Child-Pugh A and B respectively (P>0.05). Serum sodium also differed significantly between patients with MELD score ≤9 and >9 respectively (mean 143.3 mmol/L vs. 140.9 mmol/L, p<0.01).

Pearson correlation coefficients are presented in Table 2. Serum sodium demonstrated the most statistically significant correlations as it was correlated negatively with INR, aldosterone, Child-Pugh score points and MELD score. Likewise, FeNa% correlated negatively with both renin and aldosterone. On the contrary, urinary sodium values did not show any statistically significant correlations with any of the above parameters of liver function.

Discussion

Serum sodium concentration is a valid marker of hypervolemic hyponatremia developing in the late stage of liver disease. Previous investigators have shown that abnormal sodium handling is evident from the early stage of liver cirrhosis, when ascites, edema and hyponatremia are absent and this is very likely attributed to RAAS stimulation [10-12]. In the preascitic stage of cirrhosis, high sodium intake results in positive sodium balance and weight gain [13]. However, sodium retention and consequently weight gain is time-limited and a negative sodium balance was achieved after 3 weeks of high sodium intake diet (200 mmol/day) [14]. Moreover, it has been demonstrated that erect position results in decline in urinary sodium and urine output, induced by an increase in both the proximal and the distal tubular re-absorption of sodium because of intrarenal activation of the RAAS [1,13].

In the present study, we confirmed that, even in the absence of overt hyponatremia, the sodium-retaining effect of mineralocorticoids was present, since serum sodium and FeNa% correlated negatively with serum renin and aldosterone levels. The negative correlations were attributed to dilutional sodium values consequent to extracellular volume expansion [12]. Hence, cirrhotic patients without ascites appeared to have a limited fluid overload and therefore normal serum sodium.
Serum sodium concentration has long been known to be of value in determining the prognosis of patients with cirrhosis [15]. Recently, serum sodium was used for optimal allocation of donor livers and reduction in pre-transplantation mortality [8,9]. It has been reported that serum sodium could be incorporated in the MELD formula, in order to assess the risk of death more accurately, particularly in patients with low MELD score [2-6,9].

In the present study, we found that subtle divergence in serum sodium within the normal range was associated with impairment of liver function even in the early stages of cirrhosis without ascites. It was evident that the more severe the markers of liver dysfunction, such as INR, Child-Pugh and MELD scores, the lower the serum sodium concentration. FeNa% appeared to be a good marker of mineralocorticoid excess but it did not correlate with markers of liver dysfunction. Urinary sodium did not show any correlation with parameters of liver failure or portal hypertension.

We conclude that, even in the early preascitic stage of liver cirrhosis, renal sodium handling appears to be impaired and serum sodium concentration is associated with markers of liver dysfunction. Thus, serum sodium concentration appears to be a reliable surrogate marker of liver dysfunction, even in the early preascitic phase of cirrhosis.

### Table 1 Characteristics of study population according to the severity of liver disease

|                      | Child-Pugh A | Child-Pugh B | All     | p       |
|----------------------|--------------|--------------|---------|---------|
| N                    | 26           | 12           | 38      |         |
| Age (years)          | 56.7±13.0    | 58.7±10.6    | 57.3±12.2 | >0.05   |
| Alcoholic cirrhosis  | 8            | 6            | 14      | >0.05   |
| Viral Hepatitis      | 13           | 4            | 17      | >0.05   |
| Miscellaneous        | 5            | 2            | 7       | >0.05   |
| Child-Pugh score points | 5.3±0.4    | 7.7±1.1       | 6.1±1.4 | <0.001 |
| MELD score           | 8.9±1.7      | 14.3±2.5     | 10.6±3.2 | <0.001 |
| Total bilirubin (μmol/L) | 18.6±8.5 | 42.2±21.2 | 26.1±17.5 | <0.001 |
| Albumin (g/L)        | 4.0±0.4      | 3.2±0.3      | 3.7±0.5 | <0.001 |
| INR                  | 1.2±0.1      | 1.6±0.2      | 1.3±0.2 | <0.001 |
| Serum Na (mmol/L)    | 142.8±2.0    | 140.5±3.3    | 142.0±2.7 | <0.05   |
| Urinary Na (mmol/L)  | 101.9±51.2   | 82.4±50.5    | 95.9±51.1 | >0.05   |
| FeNa%                | 0.6±0.4      | 0.5±0.5      | 0.6±0.4 | >0.05   |
| Renin (μIU/mL)       | 27.5±29.7    | 64.5±121.4   | 39.2±72.7 | >0.05   |
| Aldosterone (ng/dL)  | 11.7±10.1    | 25.7±43.3    | 16.1±25.9 | >0.05   |

MELD, model for end stage liver disease; INR, international normalized ratio; FeNa, fractional excretion of sodium

### Table 2 Correlations of serum and urinary sodium with markers of liver function impairment and renin-aldosterone axis activity

|                      | Serum sodium | Urinary sodium | FeNa% |
|----------------------|--------------|----------------|-------|
| Total Bilirubin       | -0.28        | -0.07          | -0.04 |
| Albumin              | 0.30         | 0.31           | 0.13  |
| INR                  | -0.51**      | -0.09          | -0.17 |
| Renin                | -0.24        | -0.32          | -0.56*** |
| Aldosterone          | -0.40*       | -0.30          | -0.50** |
| Child-Pugh points    | -0.34*       | -0.14          | -0.06 |
| MELD score           | -0.45**      | -0.14          | -0.12 |

Serum sodium concentration has long been known to be of value in determining the prognosis of patients with cirrhosis [15]. Recently, serum sodium was used for optimal allocation of donor livers and reduction in pre-transplantation mortality [8,9]. It has been reported that serum sodium could be incorporated in the MELD formula, in order to assess the risk of death more accurately, particularly in patients with low MELD score [2-6,9]. In the present study, we found that subtle divergence in serum sodium within the normal range was associated with impairment of liver function even in the early stages of cirrhosis without ascites. It was evident that the more severe the markers of liver dysfunction, such as INR, Child-Pugh and MELD scores, the lower the serum sodium concentration. FeNa% appeared to be a good marker of mineralocorticoid excess but it did not correlate with markers of liver dysfunction. Urinary sodium did not show any correlation with parameters of liver failure or portal hypertension. We conclude that, even in the early preascitic stage of liver cirrhosis, renal sodium handling appears to be impaired and serum sodium concentration is associated with markers of liver dysfunction. Thus, serum sodium concentration appears to be a reliable surrogate marker of liver dysfunction, even in the early preascitic phase of cirrhosis.
Serum sodium in preascitic cirrhosis

Summary Box

What is already known:

- Serum sodium concentration is an established marker of liver failure in advanced chronic liver disease
- Renal sodium handling is impaired even in early preascitic phase of cirrhosis

What the new findings are:

- In the absence of overt hyponatremia, the sodium retaining effect of mineralocorticoids is present
- Serum sodium and Fractional excretion of sodium are negatively correlated with serum rennin and aldosterone levels
- Cirrhotic patients without ascites appear to have a limited fluid overload and therefore normal serum sodium concentration is maintained

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