

Evaluation of Serum Anion Gap in Patients with Liver Cirrhosis of Diverse Etiologies

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Abstract

Background: The low serum anion gap (AG) in patients with hepatic cirrhosis is generally attributed to hypoalbuminemia. Serum immunoglobulin G (IgG) (elevated in chronic viral hepatitis) and IgA (elevated in alcoholic cirrhosis) have different isoelectric points, and thus may affect serum AG in opposite directions.

Aim: To define the normal serum AG in patients with liver cirrhosis of diverse etiologies.

Study design: We retrospectively compared serum AG of 144 stable cirrhotics and 286 control patients (consecutive hospital admissions with serum creatinine concentration < 2 mg/dL).

Results: Serum AG was significantly lower among the cirrhotics, compared to the controls (5.8 ± 2.2 mEq/L vs. 7.0 ± 2.2 mEq/L, respectively, $p < 0.005$). However, when patients with serum albumin concentration < 3.5 g/dL were excluded, there was no significant difference between the cirrhotics vs controls (6.7 ± 1.8 mEq/L vs. 7.0 ± 2.2 mEq/L, $p = \text{ns}$). Moreover, patients with liver cirrhosis secondary to chronic viral hepatitis had AG similar to that of the alcoholic cirrhotics (5.6 ± 2.5 mEq/L vs. 6.0 ± 1.9 mEq/L, $p = \text{ns}$). There was a positive correlation between serum albumin concentrations > 1.9 g/dL and serum AG, and a tendency toward an inverse correlation between serum globulin concentration and serum AG.

Conclusion: Our results support the contention that hypoalbuminemia accounts for the decreased serum AG frequently observed in patients with liver cirrhosis. We found no difference in serum AG with different causes of cirrhosis. We also suggest a lower reference range for normal serum AG.

Keywords: Anion gap, acidosis, cirrhosis, acid-base.

Introduction

THE SERUM ANION GAP (AG) has traditionally received attention as a valuable clinical tool to assess acid-base status (1), and has acquired an important role in the differential diagnosis of metabolic acidosis (2). The disorders marked by a decrease in serum AG have received less attention than those associated with an increase in AG, because downward deviation occurs less often and is associated with less acutely life-threatening conditions.

Patients with liver cirrhosis have a polyclonal increase in immunoglobulins (IG) due to decreased degradation (3, 4) in the face of normal or increased synthesis of immunoglobulins. IgG paraproteins have isoelectric points (Pi) > 7.4 and therefore are positively charged at normal serum pH. It has been shown that a substantially increased level of IgG is associated with a decrease in serum AG (3, 5, 6). In contrast, the Pi of IgA is < 7.4; thus, at normal serum pH, it is more anionic, which would be expected to expand the serum AG. While patients with cirrhosis secondary to chronic viral hepatitis may have high serum IgG levels, those with cirrhosis due to alcoholic hepatitis are known to have high serum IgA levels (7). Thus, serum AG in these two groups of patients would be expected to be different.

Another feature of liver cirrhosis is hypoalbuminemia. Albumin is responsible for ~75% of the serum AG (8). Each 1 g/dL reduction in serum albumin concentration is associated with

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~2.5 mEq/L reduction in serum AG (9). Hypoalbuminemia is suggested to be the most likely explanation for the decrease in serum AG in cirrhotics (4).

In the present study, we compare the serum AG of 286 consecutive hospital admissions (controls) whose serum creatinine concentrations were < 2 mg/dL with serum AG of 144 stable patients who had biopsy-proven liver cirrhosis. We also compared the serum AG of cirrhotic patients with the diagnosis of chronic viral hepatitis with the serum AG of cirrhotic patients who had ethanol abuse.

Patients and Methods

We retrospectively analyzed the routine serum electrolytes and calcium, phosphorus, magnesium and albumin concentrations of 144 stable patients with biopsy-proven liver cirrhosis, who were being followed in the hepatology clinic at Saint Louis University Health Sciences Center. The mean (\pm SD) age of the patients was 53 ± 10 years. Eighty-seven patients were male and 57 were female. The etiologies of liver cirrhosis were as follows: chronic viral hepatitis (hepatitis B or C) in 83, ethanol abuse in 18, cryptogenic cirrhosis in 19, primary sclerosing cholangitis in 7, alpha-1-antitrypsin deficiency in 5, primary biliary cirrhosis in 3, nonalcoholic steatohepatitis in 3, autoimmune hepatitis in 2, sarcoidosis in 2, methotrexate hepatotoxicity in 1, and liver transplant failure in 1. For the control group we used 286 consecutive admissions to the hospital, during the same time period, whose serum creatinine concentrations were < 2

mg/dL. The mean age of the control group was 52 ± 18 years. Serum AG was calculated as serum concentrations of $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$. Serum electrolytes, tCO_2 and calcium concentrations were measured using ion specific electrodes (Beckman Synchron CX7 Clinical System Autoanalyzer, Brea, CA). Serum albumin concentration was measured by dye binding method using bromocresol-purple photometries. Serum PO_4 concentration was measured by ultraviolet (UV) reduction method using phosphomolibdate UV.

Statistical Analysis

The data is expressed as mean \pm SD. An unpaired student t-test was used to compare the difference between the groups ($p < 0.05$ was considered significant).

Results

The concentrations of serum AG, tCO_2 , albumin, globulin, calcium, phosphate and magnesium for the control group, all cirrhotic patients, cirrhotics due to chronic viral hepatitis (hepatitis B or C), cirrhotics due to ethanol abuse, and cirrhotics who had serum albumin concentration > 3.5 g/dL are shown in the table. The serum AG among all cirrhotics as a group was significantly lower than in the control group (5.8 ± 2.2 vs. 7.0 ± 2.2 , $p < 0.005$). However, when we excluded cirrhotics with serum albumin concentration < 3.5 g/dL, there was no significant difference between cirrhotics with albumin > 3.5 g/dL vs. control (6.7 ± 2.2 vs. 7.0 ± 2.2 , $p = \text{ns}$). The patients with cirrhosis sec-

TABLE
Comparison of Serum Anion Gap, Bicarbonate, Albumin, Globulin,
Calcium, Phosphate and Magnesium among Different Groups

	n	AG mEq/L (range)	tCO_2 mEq/L (range)	albumin g/dL (range)	globulin g/dL (range)	Ca mg/dL (range)	PO_4 mg/dL (range)	Mg mg/dL (range)
Control	286	7.0 ± 2.2 (2.0–12.0)	25.9 ± 3.0 (14.0–36.0)	4.0 ± 0.3 (1.3–4.9)	3.0 ± 0.6 (1.4–6.0)	9.6 ± 0.4 (8.6–10.5)	3.6 ± 0.7 (1.9–5.6)	-
All cirrhotics	144	$5.8 \pm 2.2^*$ (0.0–13.0)	25.6 ± 3.4 (4.1–32.0)	$3.4 \pm 0.6^*$ (1.4–4.7)	$3.6 \pm 0.8^*$ (1.9–5.4)	9.0 ± 0.6 (6.4–10.8)	3.4 ± 0.8 (1.6–7.2)	2.0 ± 0.3 (1.5–4.0)
Cirrhotics (Hepatitis B/C)	83	$5.6 \pm 2.5^*$ (0.0–13.0)	25.4 ± 3.6 (4.1–32.0)	$3.4 \pm 0.6^*$ (1.7–4.5)	$3.7 \pm 0.7^*$ (1.9–5.3)	9.0 ± 0.7 (6.4–10.8)	3.4 ± 0.9 (1.8–7.2)	2.0 ± 0.3 (1.5–4.0)
Cirrhotics (Ethanol)	18	6.0 ± 1.9 (3.0–10.0)	25.5 ± 3.4 (20.0–31.0)	$3.3 \pm 0.7^*$ (2.0–4.7)	$3.7 \pm 0.8^*$ (2.3–4.7)	9.0 ± 0.6 (8.2–9.7)	3.6 ± 0.7 (2.1–4.8)	2.1 ± 0.4 (1.6–2.7)
Cirrhotics (albumin ≥ 3.5)	65	6.7 ± 1.8 (2.0–13.0)	$26.8 \pm 2.1^*$ (22.0–32.0)	3.9 ± 0.3 (3.5–4.7)	$3.5 \pm 0.7^*$ (2.3–4.8)	9.4 ± 0.4 (8.5–10.6)	3.5 ± 0.8 (1.6–7.2)	2.0 ± 0.2 (1.6–2.7)

AG = anion gap; data presented as mean \pm SD (range); * $p < 0.05$ vs. control

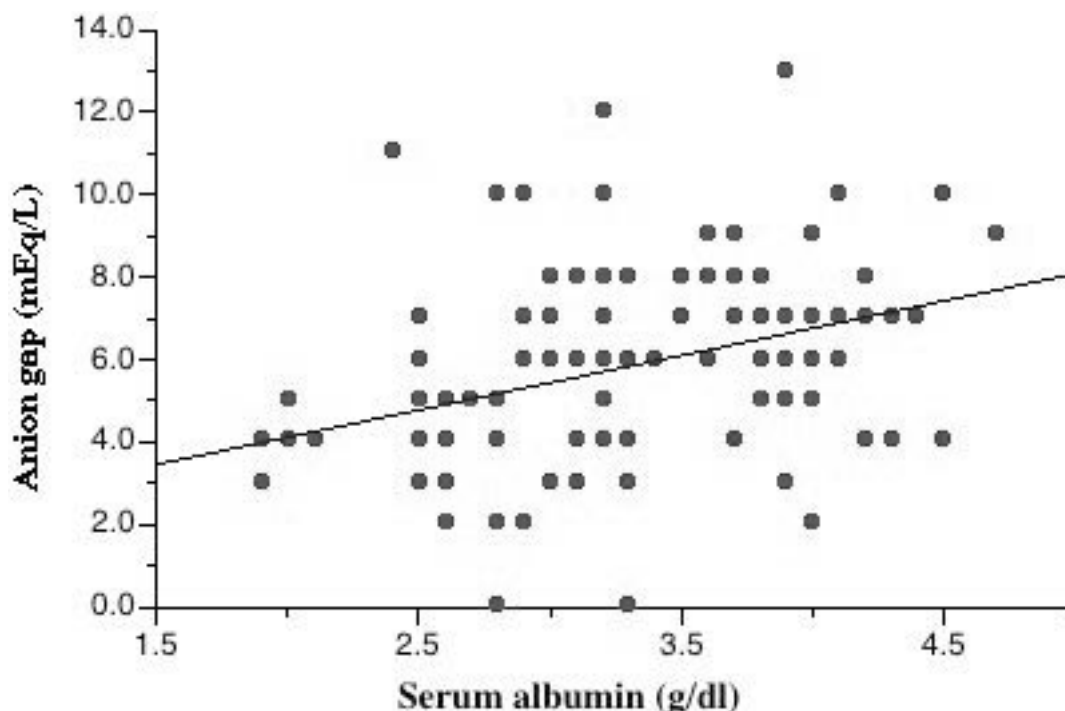


Figure. There was a positive correlation between serum AG and serum albumin concentrations > 1.9 g/dL ($r^2 = 0.2$, $p=0.0001$).

ondary to chronic viral hepatitis had a lower serum AG than those with cirrhosis due to ethanol abuse, but the difference did not reach statistical significance (5.6 ± 2.5 vs. 6.0 ± 1.9 , $p=ns$). Serum AG showed a positive correlation with serum albumin concentrations > 1.9 g/dL ($r^2 = 0.2$, $p=0.0001$, Figure), whereas there was an inverse correlation, though statistically not significant, with serum globulin concentration ($p=ns$).

Discussion

Serum AG is widely used in the evaluation of metabolic acidosis (1). A low serum AG is found in IgG multiple myeloma (5); hypoproteinemia (10); severe hyperkalemia, hypercalcemia and hypermagnesemia; and cases of acute lithium poisoning (11) or the use of other cationic drugs (12). Recently, the reference range for normal serum AG has undergone a downward shift from 12 ± 4 mEq/L (1) to 3–11 mEq/L, which is reflective of the current methods of measuring serum sodium, chloride and bicarbonate concentrations with modern ion-selective electrode technology (13). The anions normally present in serum include anionic proteins (albumin, and to a lesser extent, alpha and beta globulins), sulfate, phosphate, and organic anions. Albumin is the most abundant anionic

serum protein and is estimated to be responsible for ~75% of the serum AG (8). The synthetic function of liver is substantially affected in cirrhosis; thus, serum concentrations of albumin and other proteins synthesized in the liver (i.e., most of the alpha-1, alpha-2 and beta globulins) are markedly diminished. Therefore, cirrhotics tend to exhibit a low serum AG, which is often attributed to hypoalbuminemia (4). However, patients with cirrhosis also have higher serum concentrations of immunoglobulins. The elevated serum IgG concentrations seen in patients with chronic viral hepatitis may theoretically decrease serum AG (due to its $P_i > 7.4$), while the elevated serum IgA level seen in patients with alcoholic cirrhosis would be expected to expand serum AG (due to its $P_i < 7.4$).

In the present study we found that serum AG is significantly lower in cirrhotics as compared to the controls. However, when corrected for serum albumin concentration > 3.5 g/dL there was no significant difference. We also found a positive correlation between serum AG and serum albumin concentrations. On the other hand, we found an inverse, though insignificant, correlation between serum AG and serum globulin concentrations. Serum AG was slightly lower among patients with cirrhosis secondary to chronic viral hepatitis than among those with

cirrhosis secondary to ethanol abuse, but the difference did not reach statistical significance. That is, we found no significant difference in serum AG with different causes of liver cirrhosis (i.e., chronic viral hepatitis vs. ethanol abuse). In addition, we suggest a lower range for normal serum AG (7 ± 2 ; range 2.0–12.0 mEq/L) as was recently suggested (13).

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