CLINICAL BRIEF

Metabolic Acidosis Components in Advanced Chronic Kidney Disease: Association With Serum Albumin and Parathyroid Hormone

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Objective: To investigate the associations between the 2 main components of metabolic acidosis (unmeasured anions [UA] and hyperchloremia) with serum albumin and intact parathormone (iPTH) in patients with advanced chronic kidney disease.

Design and Methods: Cross-sectional study with advanced chronic kidney disease patients (estimated glomerular filtration rate <30 mL/minute/1.73 m^2) not receiving phosphate binders, alkali therapy, or vitamin D analogs. Arterial blood sample was collected for biochemical and blood gas analysis. UA and strong ion difference (SID) were calculated according to quantitative acid–base analysis. Reduced SID was used as a measure of hyperchloremia.

Main Outcome Measures: Serum albumin and parathormone (iPTH).

Results: A total of 383 patients were included with a mean age of 64.7 ± 16.3 year and a mean estimated glomerular filtration rate of 19.9 ± 12.1 mL/minute/1.73 m^2. Among patients with metabolic acidosis, 45.7% had metabolic acidosis exclusively because of UA and 53.7% had a hyperchloremic component (either mixed metabolic acidosis or pure hyperchloremic metabolic acidosis). Considering the main acid–base status determinants, only UA had a significant correlation with serum albumin ($r = -0.278$, $P < .001$). There was no correlation between serum albumin and SID ($r = 0.083$, $P = .156$). This is in opposition to serum iPTH, where there was no correlation with UA ($r = 0.082$, $P = .114$), but an inverse correlation between iPTH and SID was observed ($r = -0.228$, $P < .001$). Multiple linear regressions with all acid–base determinants confirmed these findings.

Conclusions: Our data brings further knowledge on the associations between metabolic acidosis with bone disorders and nutritional status, suggesting that the two main metabolic acidosis components (UA and hyperchloremia) have different effects on serum parathormone and serum albumin.

Introduction

IT IS WELL known that chronic kidney disease (CKD) causes a progressive reduction in serum bicarbonate.[1] Most patients with CKD-associated metabolic acidosis have higher serum anion gap because of the accumulation of unmeasured anions (UA); however, in many patients, CKD is also associated with hyperchloremic acidosis even in advanced stages.[2] According to the quantitative physicochemical approach to acid–base disorders, hyperchloremia leads to metabolic acidosis due to a reduction in strong ion difference (SID).[3] Previously, we have demonstrated hyperchloremia impact on metabolic acidosis of up to 43% of CKD patients.[2]

Moreover, it is known that metabolic acidosis has detrimental effects on nutrition[4] and in the pathogenesis of secondary hyperparathyroidism.[5] Several studies have demonstrated a correlation between serum bicarbonate with nutritional status and CKD-related bone disorders.[4,6–8] In the present study, we aimed to investigate the associations between the 2 main components of metabolic acidosis (UA and reduced SID) with serum albumin and iPTH.

Methods

Patient Selection

Patients were selected from a tertiary nephrology center, which provides care to a population of approximately 6 million inhabitants. After accepting to participate and signing the informed consent form, the subject was included in the study. All patients with advanced CKD (estimated glomerular filtration rate <30 mL/minute/1.73 m^2) and 24-hour protein excretion rate <3.5 g/24 hour/1.73 m^2 were initially

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included in the study. Patients receiving phosphate binders, alkali therapy, or vitamin D analogs were excluded. The study was accepted by the local ethic committee.

Blood Sampling

Laboratory analysis was carried out in arterial blood. Blood gas analysis was performed at the onsite central laboratory immediately after blood was drawn, using an AVL OMNI blood gas analyzer (Roche, Basel, Switzerland). Serum samples were frozen at −70°C, and electrolyte measurements were performed at the same moment. A Cobas Integra 700 biochemical analyzer (Roche Diagnostics GmbH, Mannheim, Germany), and standard reagents were used to measure multiple biochemical variables, including sodium, potassium, ionized calcium, phosphate, magnesium, chloride and albumin. Bicarbonate was determined according to the Henderson–Hasselbalch equation. Also, high-sensitivity C-reactive protein (hsCRP) was measured by nephelometry method.

Interpretation of Quantitative Acid–Base Analysis

The quantitative physicochemical analysis of the results was performed according to the following principles:

1. SID = $[Na^+]$ + $[K^+]$ + $[Ca^{++}]$ + $[Mg^{++}]$ − $[Cl^-]$, expressing all concentrations in milliequivalents per liter.
2. Ionic charges were calculated according to the following formulas: $Albumin_{ionized}$ (milliequivalents per liter) = albumin (gram per liter) × 0.123 × (pH − 0.631) and Phosphate (milliequivalents per liter) = phosphate (millimole per liter) × 0.309 × (pH − 0.469), expressing phosphorus in millimole per liter.
3. UA = SID − $Albumin_{ionized}$ − phosphate − $(2.46 \times 10^{pH-8} \times PCO_2)$, $Albumin_{ionized}$ and phosphate expressed in milliequivalents per liter and PCO_2 in millimeter of mercury.

Acid–Base Disturbs Definitions

These values were defined based on a control group with healthy volunteers.[9]

1. Metabolic acidosis: standard base excess (SBE) < −2 mEq/L.
2. Metabolic acidosis due to UA: SBE < −2 mEq/L, UA > 3 mEq/L, and SID > 40 mEq/L.
3. Metabolic acidosis due to hyperchloremia: SBE < −2 mEq/L, UA < 3 mEq/L, and SID < 40 mEq/L.
4. Mixed metabolic acidosis: SBE < −2 mEq/L, UA > 3 mEq/L, and SID < 40 mEq/L.

Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation or percentage. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Data with a non-normal distribution (iPTH) were log transformed. Unpaired student *t*-test was applied to compare means of continuous variables and normal distribution data. Correlations between serum albumin and iPTH with other variables were performed by Spearman rho. Two full linear regression models were performed to determine which acid–base determinants were independently correlated with serum albumin and iPTH, and *P* values < .05 were considered statistically significant. The statistical analysis was performed using SPSS 19.0 (IBM, Armonk, New York) for Windows.

Results

A total of 383 patients (57.4% males) were included in the study with a mean age of 63.7 ± 16.3 year and a mean estimated glomerular filtration rate of 19.9 ± 12.1 mL/minute/1.73 m^2. The great majority of patients were hypertensive and 148 (38.6%) had diabetes mellitus. Most of these patients (n = 335, 87.5%) had metabolic acidosis and only 1.8% had metabolic alkalosis (Table 1).

Of patients with metabolic acidosis, 153 of 335 (45.7%) had metabolic acidosis exclusively due to UA and 180 of 335 (53.7%) had a hyperchloremic component (142 had mixed metabolic acidosis—UA and hyperchloremia—and 38 had pure hyperchloremic metabolic acidosis). As expected, patients with metabolic acidosis had reduced levels of serum albumin (3.5 ± 0.6 vs. 3.2 ± 0.6, P = .026) and higher serum iPTH (222.8 vs. 134.2, P = .006). There was a trend to patients with metabolic acidosis have higher hsCRP level (4.5 ± 3.0 vs. 3.7 ± 2.2, P = .076).

The main biochemical values according to the acid–base disorder are shown in Table 2. Patients with metabolic acidosis exclusively due to UA had similar acidosis severity when compared with those patients with a hyperchloremic component (Table 2). Serum albumin was lower in patients with metabolic acidosis exclusively due to UA, and iPTH was higher in those with a reduced SID. Regarding the hsCRP, there was no difference between these groups (Table 2).

To further investigate if the 2 main components of metabolic acidosis in these patients (UA and hyperchloremia) had similar correlation with serum albumin and iPTH,

Table 1. Demographic and Clinical Data of Patients

Variable	Mean ± SD
Age (y)	64.7 ± 16.3
Male gender (%)	220 (57.4)
Arterial hypertension (%)	341 (89.0)
Diabetes mellitus (%)	148 (38.6)
eGFR (mL/min)	19.9 ± 12.1
hsCRP (mg/dL)	4.4 ± 2.8

eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein.