

Influence of Renal Function and Diet on Acid-Base Status in Chronic Kidney Disease Patients

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Objective: We investigated the influence of potential renal acid load (PRAL) and renal function on the degree of metabolic acidosis in patients with chronic kidney disease (CKD).

Design: This was a cross-sectional study.

Setting: This study was conducted at the Nephrology Outpatient Division of the Hospital Universitário Clementino Fraga Filho (Rio de Janeiro, Brazil).

Patients: Thirty CKD patients undergoing conservative treatment were divided according to plasma HCO_3^- values into acidotic ($\text{HCO}_3^- \leq 22$ mM, $n = 15$) and nonacidotic ($\text{HCO}_3^- > 22$ mM, $n = 15$).

Main Outcome Measure: Biochemical, nutritional, and anthropometric parameters and PRAL were measured.

Results: The mean of plasma HCO_3^- values was 17.7 ± 2.8 mM in the acidotic group, and 25.1 ± 2.2 mM in the nonacidotic group. There was no significant difference in mean PRAL values between the acidotic (9.8 ± 6.4 mEq/day) and nonacidotic (12.7 ± 10.0 mEq/day) groups, but there was a significant correlation between plasma HCO_3^- and creatinine clearance ($r = 0.78$, $P < .0001$). Based on the receiver operating characteristic curve, the level of creatinine clearance to begin detection of acidosis was 31.8 mL/min, with a sensitivity and specificity of 86.7%.

Conclusion: The acid-base status of this group of CKD patients undergoing conservative treatment was mainly determined by degree of renal insufficiency rather than diet.

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METABOLIC ACIDOSIS is a common manifestation of chronic kidney disease (CKD), and is associated with many adverse effects including bone disease, muscle catabolism, hypoalbuminemia, and increased risk of death.¹⁻⁴ The mechanisms underlying the development of acidosis include failure to excrete acid and the exhaustion of extracellular producing buffers, resulting in reduced serum bicarbonate, a characteristic biochemical feature of uremic acidosis. In CKD,

acidosis is believed to occur when the glomerular filtration rate decreases to <20% of normal.⁵⁻⁹ Acidosis is common in hemodialysis patients: one third to one half demonstrate predialysis serum bicarbonate levels below 22 mM. Peritoneal dialysis offers better acid-base control.^{8,10,11} However, the severity of acidosis can vary among uremic patients with a similar degree of renal dysfunction, reflecting differences in response to acidosis, as well as variability in the acid generated from the diet.^{2,3,5,9}

An accurate analysis of the acid generated from frequently consumed foods could help predict how diet affects acid-base status.^{12,13} An established method of estimating acid load involves the potential renal acid load (PRAL), developed by Remer and Manz,¹⁴ based on: (1) the estimated content of all major inorganic components of a diet (sodium, chloride, potassium, calcium, magnesium, and phosphorus), and reference values for their fractional intestinal absorption; (2) the estimated protein content of a diet with its fractional intestinal absorption, and the estimated average sulfur content in dietary protein arising from the methionine and cystine in foods; (3) the degree of dissociation of phosphates at physiologic pH

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This study was supported by Programa Institucional de Bolsas de Iniciação Científica-Conselho Nacional de Desenvolvimento Científico Tecnológico and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

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1051-2276/09/1902-0008\$36.00/0

doi:10.1053/j.jrn.2008.08.010

values; (4) the ionic valence of calcium and magnesium; and (5) the assumption of a diet-independent rate of organic acid production. The PRAL provides an estimate of the daily production of endogenous acid above the level of alkali produced (negative PRAL values are associated with fruits and vegetables). Milk and yogurt yield about 1 mEq per 100-g serving, whereas meat, fish, poultry, cheese, and even some grain products potentially yield 7 mEq per 100 g.^{12,13}

The present study investigated the influence of both PRAL and renal function on the degree of metabolic acidosis in patients with CKD undergoing conservative treatment.

Subjects and Methods

This was a cross-sectional analysis of 30 CKD patients between ages 18 and 75 years. They were treated at Hospital Universitário Clementino Fraga Filho (Rio de Janeiro, Brazil). The Ethics Committee of the hospital approved the experimental protocol, and the purpose of the study was explained before patients give written, informed consent. To be included, patients were required to have a creatinine clearance of <60 mL/min, no intake of buffering agents (calcium carbonate or sodium bicarbonate) within the previous 30 days, and the absence of inflammatory diseases, cancer, nephrotic syndrome, and immune diseases. Venous blood samples were collected in heparinized syringes to determine electrolytes and HCO_3^- . Plasma urea and creatinine were measured, and the formula of Cockcroft and Gault was used to estimate creatinine clearance.¹⁵ Patients were divided into 2 groups: acidotic ($\text{HCO}_3^- \leq 22$ mM) and nonacidotic ($\text{HCO}_3^- > 22$ mM).

Food intake, obtained from 24-hour food records, was analyzed for mean energy and protein intake calculation, using Virtual-Nutri Software (developed by the Department of Nutrition, Faculty of Public Health, University of São Paulo, São Paulo, Brazil). We calculated PRAL (Table 1) as detailed by Remer and Manz.¹⁴ Patients were treated with a protein-restricted diet containing 0.6 g/kg/day, and approximately 35 kcal/kg/day, but 60% (18 patients) admitted to not following the prescribed diet. No patients took daily water-soluble vitamin preparations.

The same trained dietician, using standard techniques, performed anthropometric measurements. These included body mass index (BMI), triceps skin-

Table 1. Average PRAL of Certain Food Groups and Combined Groups, Related to 100-g Edible Portion¹⁴

Food Group	PRAL (mEq)
Beverages	
Alkali-rich and low-phosphorus*	-1.7
Alkali-poor and low-phosphorus†	0.0
Fats and oils	0.0
Fish	7.9
Fruits and fruit juices‡	-3.1
Grain products	
Bread	3.5
Flour	7.0
Noodles, spaghetti	6.7
Meat and meat products	9.5
Milk and dairy products	
Milk and noncheese products	1.0
Cheeses with lower protein content§	8.0
Cheeses with higher protein content¶	23.6
Vegetables	-2.8
Potatoes	-4.0

PRAL, potential renal acid load.

*Beverages (phosphorus <30 mg/100 g) with several times higher sodium + potassium content compared with chloride. Examples: red wine, white wine, certain mineral (soda) waters, and coffee.

†Beverages (phosphorus <30 mg/100 g) with similar sodium + potassium versus chloride content.

‡Without dried fruits.

§Less than 15 g protein/100 g.

¶More than 15 g protein/100 g.

||Without asparagus (very low alkali excess) and spinach (very high alkali excess).

fold (TSF), midarm circumference, and midarm muscle area (MMA). Body mass index was calculated as body weight divided by squared height, and the cutoff points were those recommended by the World Health Organization.¹⁶ Triceps skinfolds were measured to the nearest millimeter, using a Lange Skinfold Caliper (Cambridge Scientific Industries, Inc., Cambridge, MA) and 3 sets of measurements were averaged. The MMA was calculated from the following equation: $\text{MMA} = [(\text{midarm circumference (cm)} - \pi \times \text{TSF (mm)} \div 10)^2 \div 4] - n$, where $n = 10$ for males, and 6.5 for females. The TSF and MMA were classified in percentiles according to age and gender, as proposed in the National Health and Nutrition Examination Survey II. Muscle and fat-mass wasting were defined as values less than the 15th and 5th percentiles, respectively.¹⁷

Statistical Analysis

Results are expressed as mean \pm standard deviation or as a percentage. Student's *t*-test was used to

Table 2. Differences Between Acidotic and Nonacidotic Groups

Parameters	Acidotic (n = 15)	Nonacidotic (n = 15)	P Value
Age (y)	62.1 ± 11.2	66.0 ± 11.0	.368
Gender (% men)	46.6	53.3	
Creatinine clearance (mL/min)	24.5 ± 8.2	42.9 ± 10.8	.020
HCO ₃ ⁻ (mM)	17.7 ± 2.8	25.1 ± 2.2	<.001
PRAL (mEq/day)	9.8 ± 6.4	12.7 ± 10.0	.974
Energy intake (kcal/kg)	21.6 ± 6.6	21.4 ± 6.9	.242
Protein intake (g/kg)	0.92 ± 0.53	1.02 ± 0.37	.172
BMI (kg/m ²)	25.8 ± 4.9	27.2 ± 3.2	.355
MMA (cm ²)	37.1 ± 11.9	40.5 ± 11.2	.425
TSF (mm)	17.6 ± 11.6	17.2 ± 8.0	.122

PRAL, potential renal acid load; BMI, body mass index; MMA, midarm muscle area; TSF, triceps skinfold.

examine the difference between means. The Pearson correlation coefficient was used to examine the relationship between variables, and prediction values relating acidosis to creatinine clearance were established using the receiver operating characteristic curve. Statistical significance was accepted as $P < .05$. Statistical analyzes were performed using the program SPSS version 11.0 (Chicago, IL).

Results

The mean age of the study population was 64.4 ± 11.2 years, 50% of whom were men. The mean creatinine clearance was 33.7 ± 13.3 mL/min, and the main causes of CKD were hypertensive nephrosclerosis (43.3%), followed by diabetic nephrosclerosis (23.3%), polycystic kidney disease (20.0%), chronic glomerulonephritis (6.7%), and other diseases or unknown causes (6.7%). A plasma bicarbonate concentration ≤ 22 mM, compatible with metabolic acidosis, was observed in 50% of patients. These acidotic patients were compared with nonacidotic patients (based on higher HCO₃⁻ values). Our analysis of the two groups showed that the mean HCO₃⁻ was 17.7 ± 2.8 mM in acidotic patients, and 25.1 ± 2.2 mM in nonacidotic patients ($P < .001$). The average creatinine clearance was significantly lower in acidotic patients ($P = .02$; Table 2).

The BMI values were not statistically different among groups: 50% of subjects were overweight, i.e., 15 patients had a BMI > 25 kg/m². Values for MMA and TSF were not different between groups, but the prevalence of muscle and fat-mass wasting was higher in the acidotic group (28.5% and 21.4%, respectively). No nonacidotic patient had fat-mass wasting, and only 15.4% had muscle-mass wasting. Mean energy, protein

intake, and PRAL did not differ between groups: 60% of acidotic patients and 80% of nonacidotic patients had protein intake levels > 0.8 g/kg/day. Anthropometric measurements and dietary intake were not correlated with plasma HCO₃⁻.

Finally, we found a significant correlation between creatinine clearance and plasma bicarbonate level ($r = 0.78$, $P < .0001$; Fig. 1). On the other hand, there was no correlation between degree of acidosis and PRAL ($r = 0.18$, $P = .332$). The cutoff point for creatinine clearance, i.e., the level at which the association with acidosis begins to strengthen, was 31.8 mL/min. This level, as assessed by the receiver operating characteristic curve (Fig. 2), had a sensitivity of 86.7% (95% confidence interval [CI], 59.5% to 98.0%) and a specificity of 86.7% (95% CI, 59.5% to 98.0%). The area under the receiver operating characteristic curve was 0.933, and the standard error was 0.0489 (95% CI, 0.779 to 0.990).

Discussion

Our results indicate a high prevalence of metabolic acidosis in patients undergoing conservative

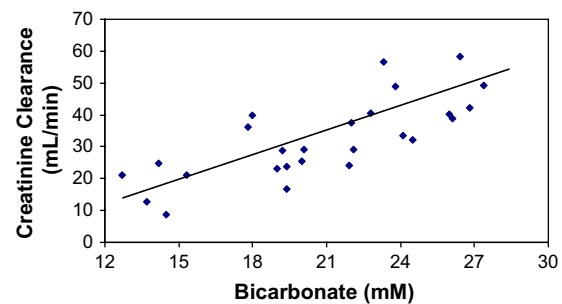


Figure 1. Correlation between creatinine clearance and bicarbonate level ($r = 0.78$, $P < .0001$).

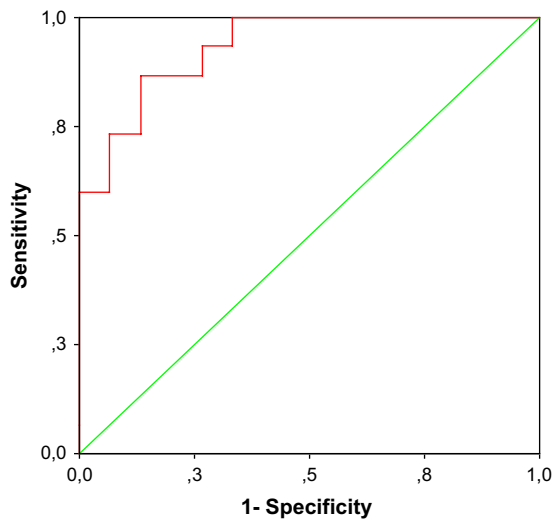


Figure 2. Receiver operating curve plot of creatinine clearance level. Area under the receiver operating curve: 0.933 (SE, 0.0489; 95% CI, 0.779 to 0.990). The diagonal line indicates line of no discrimination.

treatment, i.e., dietary manipulation. This is important, because a modest degree of metabolic acidosis can be harmful and may initiate a series of maladaptive responses, such as loss of lean body mass via alterations in hormone systems (reduced release of growth hormone, or induction of insulin resistance and reduced thyroid function³). The catabolic mechanisms activated by metabolic acidosis include: (1) activation of caspase-3, performing an initial cleavage of muscle proteins;^{18–21} (2) stimulation of the ubiquitin-proteasome system to break down muscle proteins;^{1,3,22,23} (3) insulin resistance, which accelerates muscle protein degradation by activating caspase-3 and the ubiquitin-proteasome system;²⁴ (4) increased levels of inflammatory cytokines that could activate the ubiquitin-proteasome system and muscle wasting;^{1,3,25,26} and (5) activation of the rate-limiting enzyme for the irreversible decarboxylation of leucine, isoleucine, valine, branched-chain ketoacid dehydrogenase in muscles.^{1,3,27} Dietary intervention is a major component of CKD therapy. Its aim is to minimize uremic symptoms by limiting the accumulation of nitrogenous waste products.²⁸ In addition, dietary protein restriction is recommended for patients with CKD, and is expected to slow the progression of renal failure.^{1,29–31}

Patients with poorly functioning kidneys develop metabolic acidosis because of an impaired renal capacity to excrete the acid produced daily. They can benefit from specific dietetic changes

designed to reduce daily acid production.¹² The diet can be designed more easily by calculating the PRAL, to modulate daily acid production. Fruits and vegetables have negative PRAL values, whereas protein-rich foods have positive values. Consequently, the daily intake of acid equivalents can be reduced through: (1) the exchange of certain protein-rich foods for alkali-rich foods; (2) the addition of buffer-containing foods, such as fruits or vegetables, to a high protein diet; and (3) a selection of different protein sources. In the present study, we did not find differences in the average PRAL between acidotic and nonacidotic patients. The most likely explanation for this finding is that all patients were assigned the same protein-restricted diet, and even though compliance was not optimal, the similarity in the amounts and sources of protein eaten by the 2 groups was fundamental in the lack of difference in PRAL. Underestimation or overestimation of food intake is another potential explanation, as is the nutrient variation in natural foods and in different kinds of food-processing and preparation. Finally, there can be variation in nutrient absorption rates between individuals. More studies will be necessary to assess potential mechanisms.

The major determinant of metabolic acidosis in these predialysis patients was their degree of renal insufficiency. Evidence for this conclusion involves the high correlation between plasma bicarbonate and creatinine clearance. Metabolic acidosis was observed in 50% of patients who had creatinine clearance values of <60 mL/min, and the level below which acidosis had a stronger association was 31.8 mL/min. There is no consensus about the level of renal insufficiency associated with the detection of metabolic acidosis, and the analysis of the third annual National Health and Nutrition Examination Survey III (1988 to 1994) concluded that a detectable decrease in plasma bicarbonate concentrations in women was not present until creatinine clearance was <20 mL/min.³² Other reports^{5,7–9} and our data support the importance of routine screening for metabolic acidosis at stage III of CKD.²⁹

The prevalence of muscle and fat-mass wasting was higher in acidotic patients, although their protein intake was above the recommended daily allowance. These results are consistent with the conclusion that a loss of lean body mass in CKD patients is likely the result of complications of CKD, and thus will not be cured simply by increasing dietary protein.^{1,28} Even when CKD patients ate a very low-protein diet, a neutral nitrogen

balance and normal levels of both serum proteins and anthropometric estimates of lean body mass were present as long as the acidosis was corrected. Moreover, Cupisti et al.³⁰ found no major abnormality in nutritional status or muscle mass in patients with advanced CKD treated with moderate to severe protein restriction.

Conclusion

There was no correlation between degree of acidosis and PRAL. However, the decrease in renal function was the main determinant of metabolic acidosis, appearing when creatinine clearance reached 31.8 mL/min. This study suggests that acid-base status should be monitored from stage III of CKD.

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