

Potassium Bicarbonate Reduces Urinary Nitrogen Excretion in Postmenopausal Women

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ABSTRACT

Previously we demonstrated that low grade chronic metabolic acidosis exists normally in humans eating ordinary diets that yield normal net rates of endogenous acid production (EAP), and that the degree of acidosis increases with age. We hypothesize that such diet-dependent and age-amplifying low grade metabolic acidosis contributes to the decline in skeletal muscle mass that occurs normally with aging. This hypothesis is based on the reported finding that chronic metabolic acidosis induces muscle protein breakdown, and that correction of acidosis reverses the effect. Accordingly, in 14 healthy postmenopausal women residing in a General Clinical Research Center and eating a constant diet yielding a normal EAP rate, we tested whether correcting their "physiological" acidosis with orally administered potassium bicarbonate (KHCO_3 ; 60–120 mmol/day for 18 days) reduces their urinary nitrogen loss. KHCO_3 reduced EAP to

nearly zero, significantly reduced the blood hydrogen ion concentration ($P < 0.001$), and increased the plasma bicarbonate concentration ($P < 0.001$), indicating that pre- KHCO_3 , diet-dependent EAP was significantly perturbing systemic acid-base equilibrium, causing a low grade metabolic acidosis. Urinary ammonia nitrogen, urea nitrogen, and total nitrogen levels significantly decreased. The cumulative reduction in nitrogen excretion was 14.1 ± 12.3 g ($P < 0.001$). Renal creatinine clearance and urine volume remained unchanged. We conclude that in postmenopausal women, neutralization of diet-induced EAP with KHCO_3 corrects their preexisting diet-dependent low grade metabolic acidosis and significantly reduces their urinary nitrogen wasting. The magnitude of the KHCO_3 -induced nitrogen-sparing effect is potentially sufficient to both prevent continuing age-related loss of muscle mass and restore previously accrued deficits. (*J Clin Endocrinol Metab* 82: 254–259, 1997)

IN DISORDERS that cause chronic metabolic acidosis, protein degradation in skeletal muscle is accelerated (1–3), increasing the production of nitrogen (N) end products that are eliminated in the urine, thereby inducing negative N balance (3). This disturbance of N metabolism apparently results directly from the acidosis, not from its cause or from other sequelae of the underlying acidosis-producing disorder, because it occurs with widely differing acidosis-producing conditions (2–7), and it is reversible by administration of alkali (8–11), which corrects the acidosis but not its cause. Acidosis-induced proteolysis appears to be an acid-base homeostatic mechanism. By releasing increased amounts of amino acids, in particular glutamine, which is used by the kidney for synthesis of ammonia, the kidney can increase the excretion of acid (as ammonium) in the urine, thereby mitigating the severity of the acidosis (2, 3, 12, 13).

One cause of chronic metabolic acidosis is eating a diet whose metabolism yields noncarbonic acids (e.g. sulfuric acid) in excess of base (e.g. bicarbonate) (14). Such diets induce a chronic low grade metabolic acidosis even in healthy subjects; the severity of the acidosis correlates with the net rate of endogenous acid production (acid minus base) (14, 15). Net acid-producing diets are typical of those ingested by the inhabitants of industrialized countries (14, 15), where consumption of foods rich in acid precursors (animal foods) is disproportionate to that of foods rich in base precursors (vegetable foods). Habitual ingestion of such diets

has been linked to clinical disorders, in particular nephrolithiasis and osteoporosis, in which diet-induced acid production has been identified as contributing to their pathogenesis (16–19).

Because of the attendant low grade chronic acidosis, habitual ingestion of typical net acid-producing diets might chronically sustain a slightly increased state of protein breakdown and consequent N wasting. Conceivably, low grade N wasting is a tonic "normal" state in adult humans, accounting for the normal progressive decrease in muscle mass as adults get older (20, 21). Indeed, diet-dependent acidosis-induced muscle wasting might be amplified by age because diet-dependent metabolic acidosis tends to increase in severity with age (22, 23), which, in turn, appears to result from the normal age-related decline in the function of the kidney (24).

These considerations prompted us to investigate, in healthy adult subjects eating a normal net acid-producing diet, whether mitigation of the normal dietary net acid load influences urinary N excretion.

Materials and Methods

In 14 healthy postmenopausal women residing in the University of California-San Francisco General Clinical Research Center and eating a constant net acid-producing diet, we tested the effect of reducing the dietary net acid load on the rate of excretion of N in the urine. We reduced the diet acid load without changing the diet composition, by administering a dietary supplement of the absorbable base, potassium bicarbonate (KHCO_3). The protocol was approved by the University of California-San Francisco committee on human research, and informed consent was obtained from each woman. The women ranged in age from 51–77 yr, in weight from 53–76 kg, in height from 153–175 cm, and in body mass index from 21–28 kg/m². All were at least 5 yr postmenopausal, and none was taking estrogen.

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Each woman ate a constant diet (per 60 kg BW), containing 96 ± 1 g protein (15.4 g N) and 1995 ± 17 Cal, which yielded an endogenous acid production rate of 1.25 mEq/kg BW (normal range, 0.5–1.5 mEq/kg BW). The diet was begun approximately 2 weeks before the control period, before the collection of specimens for measurements of plasma and urine acid-base, electrolyte, and N composition was initiated, to establish a steady state on the specific diet (adaptation period). Light activity levels were maintained throughout the study. After a subsequent 6-day control period, oral KHCO₃ was given as a dietary supplement at a dose of 60–120 mmol/day for 18 days (KHCO₃ period). Balance studies were continued for an additional 12 days after KHCO₃ was stopped (recovery period).

Sample collection

Arterialized venous blood samples were collected between 1530–1630 h, at least 3 h after the noon meal, without stasis or exposure to air, from a vein on the back of the hand, which was warmed in a water bath at 44 C for 5 min. Blood specimens were obtained on 18 of 29 days throughout the study. The specimens were analyzed for blood pH and carbon dioxide tension, plasma total carbon dioxide content, blood urea N, and serum creatinine.

Each voided urine specimen was maintained under a thin layer of mineral oil, preserved with thymol, and pooled in 24-h collections for determination of pH and carbon dioxide content. In addition, the total volume and the concentrations of ammonium, titratable acid, creatinine, and urea were measured.

Analytical methods

Analytical methods for measuring blood and urine acid-base parameters have been previously described (16, 23). Net acid excretion was calculated as the sum of the excretion rates of titratable acid and ammonium minus that of bicarbonate. The titratable acid concentration was determined by titration, and the urinary ammonium concentration was determined by the phenol method. Blood urea N was determined by enzymatic reaction, and blood and urinary creatinine were measured by the Jaffe method. Total N was calculated as the sum of urea N, creatinine N, and ammonium N.

Statistical analysis

For each blood and urine variable, the all-subject averages were computed for each day and used as the primary database. The results were analyzed by paired *t* tests and by linear, nonlinear, and multiple regression analysis using Sigmastat (Jandel Co., San Raphael, CA) and Statistica (Statsoft, Tulsa, OK). The results are presented as the mean \pm SD.

Results

During the control period before KHCO₃ administration, all measured variables were stable, including the urinary excretion rates of urea, creatinine, ammonia, total N, and net acid; blood hydrogen ion ($[H^+]_b$) and plasma bicarbonate concentrations ($[HCO]_p$; Figs. 1-3); and serum urea and creatinine concentrations.

During KHCO₃ administration, $[H^+]_b$ decreased and $[HCO]_p$ increased significantly, from 40.2 ± 2.2 to 38.1 ± 1.7 nEq/L ($P < 0.001$) and from 24.2 ± 1.5 to 25.9 ± 1.5 mEq/L ($P < 0.001$), respectively. Net acid excretion decreased from 75.0 ± 9.7 to 10.2 ± 26.9 mEq/day ($P < 0.001$; Table 1 and Fig. 3). Urinary ammonium N (NH₄ N), urinary urea N (UUN), and total N excretion decreased significantly: NH₄ N, 671 ± 83 to 287 ± 90 mg/day ($P < 0.001$); UUN, $12,967 \pm 604$ to $12,551 \pm 451$ mg/day ($P < 0.05$); and total N, $13,988 \pm 625$ to $13,193 \pm 510$ mg/day ($P < 0.001$; Table 1 and Fig. 4). Over the 18-day KHCO₃ supplementation period, the cumulative reduction in urinary N excretion was 14.4 g.

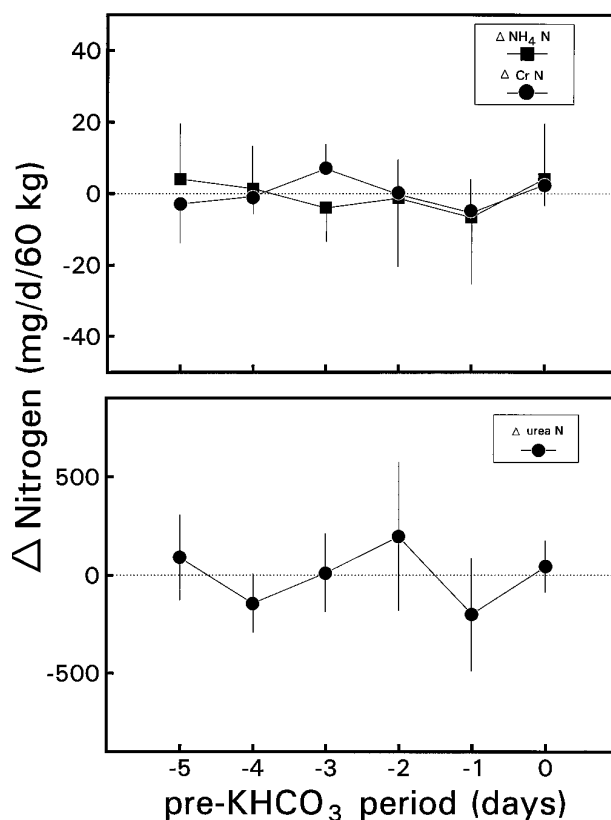


FIG. 1. Demonstration that the urinary excretion rates of the components of urinary N (urea, ammonia, and creatinine) were stable before KHCO₃ administration was begun (n = 14 subjects).

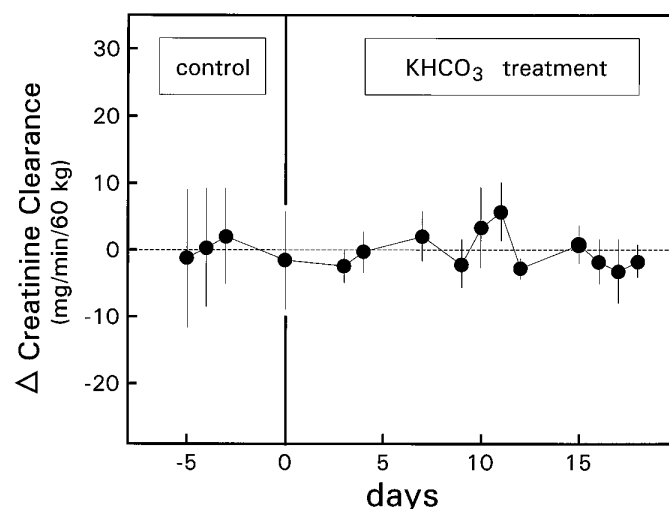


FIG. 2. Demonstration that creatinine clearance did not change during the period of KHCO₃ administration (n = 14 subjects).

Consider that magnitude of cumulative N reduction in terms of lean body mass (LBM). One kilogram of LBM is equivalent to 32 g N (25). Therefore, 14 g N in 18 days is equivalent to 0.43 kg LBM ($14 \text{ g N} \div 32 \text{ g N/kg LBM}$) in 18 days. In women, LBM, which is predominately skeletal muscle, decreases by about 0.22 kg/yr (20) or about 10.8 g/18 days ($0.22 \text{ kg/yr} \times 1000 \text{ g/kg} \times 1 \text{ yr}/365 \text{ days} \times 18 \text{ days}$). Thus, the KHCO₃-induced cumulative reduction in N excre-

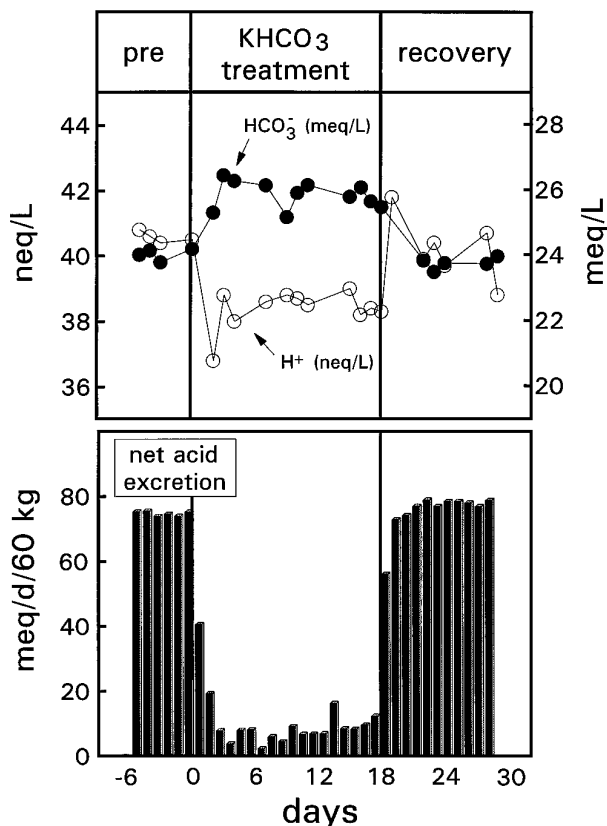


FIG. 3. Lower panel, Sustained administration of KHCO₃ (1–2 mEq/kg BW) reduced urinary net acid excretion to nearly zero and, therefore, presumably neutralized almost all of the daily net endogenous noncarbonic acid production. Upper panel, Concurrently with the elimination of the endogenous acid load, [H⁺]_b decreased and [HCO₃⁻]_p increased, which indicates that the normal endogenous acid load before KHCO₃ administration was sufficient to significantly acidify the extracellular fluid compartment (*viz.* induce a low level metabolic acidosis).

TABLE 1. Summary of Results

Index	Before KHCO ₃ supplementation	During KHCO ₃ supplementation	After KHCO ₃ supplementation
Blood			
pH	7.39 ± 0.02	7.41 ± 0.02 ^a	7.40 ± 0.03 ^b
[HCO ₃ ⁻] _p (meq/L)	24.2 ± 1.5	25.9 ± 1.5 ^a	23.8 ± 1.3 ^{b,c}
BUN (mg/dL)	20.9 ± 2.6	20.9 ± 2.4	20.1 ± 3.1
Urine			
Cr N (g/day)	0.92 ± 0.22	0.95 ± 0.12	0.97 ± 0.11 ^d
Cr Cl (mL/min)	90 ± 21	91 ± 17	98 ± 21 ^{d,e}
NH ₄ N (g/day)	0.67 ± 0.08	0.29 ± 0.09 ^a	0.68 ± 0.09 ^b
Urea N (g/day)	13.0 ± 0.60	12.6 ± 0.45 ^c	12.4 ± 0.83 ^c
Urea Cl (mL/min)	43.6 ± 6.8	45.3 ± 7.1	45.2 ± 8.8
Total N (g/day)	14.0 ± 0.63	13.2 ± 0.51 ^a	13.5 ± 0.84 ^d
NAE (meq/day)	75.0 ± 9.7	10.2 ± 26.9 ^a	75.0 ± 11.5 ^b
Vol (L/day)	2.98 ± 0.32	2.98 ± 0.36	3.04 ± 0.36

All values were calculated per 60 kg.

^a *P* < 0.001 *vs.* before KHCO₃.

^b *P* < 0.001 *vs.* after KHCO₃.

^c *P* < 0.05 *vs.* before KHCO₃.

^d *P* < 0.01 *vs.* before KHCO₃.

^e *P* < 0.01 *vs.* after KHCO₃.

tion was sufficient to completely offset the expected age-related cumulative N loss over the same period, with 3.2 g N to spare. Extrapolating that 3.2 g net gain over 1 yr would

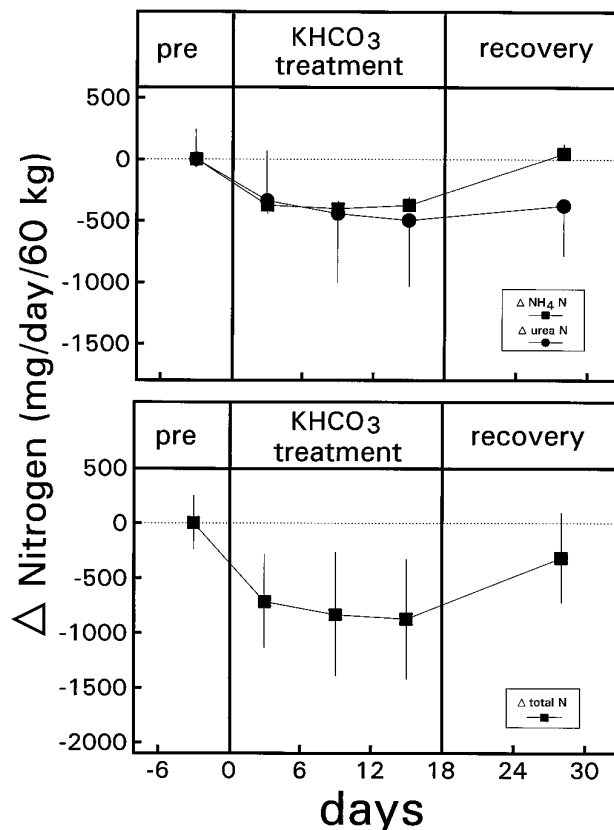


FIG. 4. Demonstration that the daily urinary excretion rates of both urea and ammonia N decreased significantly during KHCO₃ administration, as did total N excretion (calculated as the sum of urea, ammonia, and creatinine N). Results were analyzed in 6-day pools. During the KHCO₃ administration period, the daily N retained was 0.78 g/day, and the cumulative gain was approximately 14 g.

result in a net gain of LBM of 2.0 kg (3.2 g N/18 days × 365 days/yr × 1 kg LBM/32 g N), which would amount to a restoration of about 1 decade of muscle mass decline. Thus, the magnitude of the KHCO₃-induced N-sparing effect is potentially sufficient to both prevent continuing loss of muscle mass and restore previously accrued deficits.

KHCO₃ supplementation had no significant effect on serum creatinine, urinary creatinine, creatinine clearance, serum urea N, urea clearance, or urine volume (Table 1 and Fig. 2). Mean body weight was unchanged (+0.2 ± 0.4 kg; *P* = NS).

When the KHCO₃ supplement was stopped, [H⁺]_b, [HCO₃⁻]_p, and net acid excretion promptly returned to baseline (Table 1 and Fig. 3). Within the period of observation, NH₄ N excretion returned to baseline, and UUN and total N excretion started to increase (Table 1 and Fig. 4).

Discussion

The findings of the present study indicate that in healthy postmenopausal women: 1) reducing the diet net acid load from normal to nearly zero with exogenous base (KHCO₃) significantly reduces blood acidity and increases the plasma bicarbonate concentration, indicating that the unsupplemented normal diet net acid load was significantly perturbing systemic acid-base equilibrium, causing a low grade met-

abolic acidosis; 2) correction of the diet-dependent metabolic acidosis causes a significant reduction in urinary N excretion, comprising nearly equal reductions in urinary ammonia and urea excretion; and 3) this N-sparing effect is reversed by withholding the exogenous base.

Because blood acidity decreased significantly and plasma bicarbonate increased significantly when the diet-dependent net acid load was eliminated, the preexisting net acid load must have been significantly perturbing systemic acid-base equilibrium, in effect causing a low grade metabolic acidosis. Because American diets typically yield positive nonzero rates of net endogenous acid production (14), and because the functional integrity of the kidneys progressively declines during adulthood (24), chronic low grade age-related metabolic acidosis is the norm in adult humans. When the net acid load increases from zero to values typical of American net acid-producing diets, the kidney increases net acid excretion to a new steady state approaching the new net acid load, thus stabilizing blood acid-base equilibrium, but not before a new steady state has developed with significantly greater blood acidity and lower plasma bicarbonate concentrations, the levels of which are determined in part by the magnitude of the acid load and the prevailing functional integrity of the kidney. Failure to recognize the respective roles of the diet net acid load and the age-related impaired renal acid-base regulatory integrity has prevented recognition of the low grade acidotic state that exists in otherwise healthy adults, whose acidotic plasma acid-base composition traditionally has been viewed as normal. Rather, the truly nonacidotic state is defined as the plasma acid-base composition when the diet net acid load is zero and renal function is unimpaired, as in young adulthood.

It is understandably difficult to think "metabolic acidosis" when the values for plasma acid-base composition are in the range traditionally considered normal. As the term metabolic acidosis implies pathophysiological sequelae, if such sequelae were not present with normal diet net acid loads one might remain skeptical despite the arguments presented above, but, in fact, such acidosis-induced pathophysiological conditions as negative calcium and phosphorus balance and accelerated bone resorption appear to be a consequence of the normal diet acid load and are significantly improved by normalizing blood acid-base composition by neutralizing the diet net acid load with small amounts of exogenous base (16). As Alpern (26) has noted, the degree of metabolic acidosis manifested by the plasma acid-base composition underestimates the severity of the pathophysiological injury caused by the acid-base disturbance. With diet-dependent chronic metabolic acidosis, renal and extrarenal homeostatic adaptations occur that serve to minimize disturbances in $[H^+]_b$ and $[HCO]_p$, but these adaptations themselves are detrimental. Those include decreased renal citrate production and excretion (27), hypercalciuria (28), dissolution of bone (29), protein catabolism and muscle wasting (1–3), and progression of renal disease (30). Thus, homeostatic mitigation of the disturbance of extracellular acid-base equilibrium requires the body to accept certain deleterious trade-offs (26). Although the degree of diet-dependent metabolic acidosis is mild as judged by the degree of perturbation of blood acid-base

equilibrium, it cannot be considered mild as judged by its negative biological effect.

Chronic metabolic acidosis is a recognized cause of renal N wasting. N loss occurs both in conditions in which net endogenous acid production is abnormally high, such as chronic ketoacidosis induced by dietary carbohydrate deficiency (4, 5), and in conditions in which the endogenous acid load is not increased but the acid excretory and/or bicarbonate reabsorptive capacity of the kidney is impaired, such as the acidosis caused by advanced renal insufficiency (2, 3, 6, 7). In both conditions, the N wasting and attendant negative N balance are reversed on correction of acidosis by the administration of exogenous alkali (8–11). Consistent with that effect of alkali, in children with chronic renal acidosis, correction of acidosis with alkali therapy reverses growth retardation and permits the attainment and maintenance of normal stature (31).

Metabolic acidosis induces N wasting in part by directly increasing the rate of protein degradation in skeletal muscle without commensurately increasing the rate of protein synthesis (1, 2). That proteolytic effect has been attributed to two acidosis-induced disturbances in skeletal muscle cells: stimulation of an ATP- and ubiquitin-dependent proteolytic pathway (32) and enhancement of the oxidation of proteolytically released branched chain amino acids (valine, leucine, and isoleucine), preventing their reuptake for protein synthesis (33–35). Nonbranched chain amino acids, especially glutamine, released into the circulation in increased supply, are made available to the kidney for the generation and excretion of ammonium, thereby eliminating muscle N and precluding its reuse for protein synthesis (2, 3, 12, 13).

Additional mechanisms operate during chronic metabolic acidosis to facilitate renal excretion of ammonium and promote N wasting. Chronic metabolic acidosis causes an adaptive increase in renal glutamine extraction and ammonia production (36). Glutamine becomes the major source of the increased ammonium excreted in the urine. Acidosis also stimulates hepatic production of glutamine, which serves to sustain the acidosis-augmented rates of renal glutamine extraction and utilization (7, 37–39).

Consistent with the above considerations, in our subjects, correction of diet-dependent acidosis was accompanied by a reduction in urinary ammonium excretion, which returned to control when the acidosis was allowed to recur by discontinuing the KHCO₃ supplement. However, in addition to the reduction in NH₄ N excretion during KHCO₃ administration, a sustained reduction in UUN excretion also occurred, suggesting that the higher pretreatment excretion rates of urea were contributing to the acidosis-induced N wasting. The reductions in urea and ammonia excretion contributed about equally to the N-sparing effect.

Because no detectable reduction occurred in creatinine clearance with KHCO₃ administration, the observed reduction in urea excretion was not attributable to a reduced filtered load of urea caused by a reduced glomerular filtration rate. Similarly, because urine flow was not reduced, reduced urea excretion was not attributable to increased passive urea absorption secondary to increased renal water reabsorption. Otherwise, assuming a urea distribution space equal to total body water, the resultant near doubling of the serum urea N

concentration would have been easily detected. Alternatively, if the reduction in urea excretion was due to reduced endogenous net urea production, the requisite reduction in serum urea N (<0.4 mg/dL) would have been too small to observe. Accordingly, the reduction in urea excretion during KHCO_3 administration is consistent with a reduced net rate of urea production, but inconsistent with either reduced a glomerular filtration rate or increased renal urea reabsorption.

We believe that the most straightforward interpretation of the findings in this study is this. KHCO_3 administration reduced the net endogenous acid production and corrected the preexisting low grade metabolic acidosis, raising urine pH and reducing the total rate of renal ammonia production. As a consequence, both the excretion of ammonia in the urine and the delivery of ammonia to the systemic circulation via the renal vein decreased. The reduction in urinary ammonia contributed directly to the improvement in N balance. The reduction in ammonia delivery to the systemic circulation via the renal vein in addition contributed indirectly to improvement in N balance by limiting substrate (*viz.* ammonia) availability for hepatic urea production (40), thereby reducing external loss of N as urinary urea. In addition, by correcting the preexisting low grade metabolic acidosis, KHCO_3 decreased the pretreatment rate of muscle proteolysis, thereby limiting the availability of amino acids for both urea and ammonia production, further contributing to the improvement in N balance.

Reduction of urea excretion during alkali administration has been observed in other acidotic states. Papadoyannakis *et al.* (8) reported significant reductions in urinary urea and total urinary N excretion in response to sodium bicarbonate administration in patients with renal acidosis. In fasting subjects with ketoacidosis, administration of bicarbonate salts reduced urea N excretion significantly in some studies (9), but not in others (10, 11). Hannaford *et al.* (9) reported a significant reduction in urinary urea excretion in response to the administration of combined sodium bicarbonate and potassium chloride in fasting obese subjects with ketoacidosis. Gougeon-Reyburn *et al.* (10, 11), using a very low calorie diet (<500 Cal) made up almost exclusively of protein, found no significant change in urea excretion in response to either sodium or KHCO_3 . The reason for the difference in response of urea excretion between the studies of Hannaford and Gougeon-Reyburn is not clear.

Whether the renal N-sparing effect of KHCO_3 administration translates to improved whole body N balance is not specifically answered in this study because we did not also measure fecal N excretion. Fecal N excretion is a small fraction (<12%) of the total N excretion (25), however, and does not change with alkali administration (8). Papadoyannakis *et al.* (8) found no change in daily measured stool N losses during sodium bicarbonate treatment of patients with renal acidosis, although urinary N excretion decreased significantly. Further studies are necessary to determine the effects of KHCO_3 administration on N balance and LBM.

Acknowledgments

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