IMPROVED MINERAL BALANCE AND SKELETAL METABOLISM IN POSTMENOPAUSAL WOMEN TREATED WITH POTASSIUM BICARBONATE

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Abstract *Background.* In normal subjects, a low level of metabolic acidosis and positive acid balance (the production of more acid than is excreted) are typically present and correlate in degree with the amount of endogenous acid produced by the metabolism of foods in ordinary diets abundant in protein. Over a lifetime, the counteraction of retained endogenous acid by base mobilized from the skeleton may contribute to the decrease in bone mass that occurs normally with aging.

Methods. To test that possibility, we administered potassium bicarbonate to 18 postmenopausal women who were given a constant diet (652 mg [16 mmol] of calcium and 96 g of protein per 60 kg of body weight). The potassium bicarbonate was given orally for 18 days in doses (60 to 120 mmol per day) that nearly completely neutralized the endogenous acid.

Results. During the administration of potassium bicarbonate, the calcium and phosphorus balance became less negative or more positive — that is, less was excreted in comparision with the amount ingested (mean [±SD] change in calcium balance, +56±76 mg [1.4±1.9 mmol] per day per 60 kg; P = 0.009; change in phosphorus balance, +47±64 mg [1.5±2.1 mmol] per day per 60 kg; P = 0.007) because of reductions in urinary calcium and phosphorus excretion. The changes in calcium and phosphorus balance were positively correlated (P<0.001). Serum osteocalcin concentrations increased from 5.5±2.8 to 6.1±2.8 ng per milliliter (P<0.001), and urinary hydroxyproline excretion decreased from 28.9±12.3 to 26.7±10.8 mg per day (220±94 to 204±82 μmol per day; P = 0.05). Net renal acid excretion decreased from 70.9±10.1 to 12.8±21.8 mmol per day, indicating nearly complete neutralization of endogenous acid.

Conclusions. In postmenopausal women, the oral administration of potassium bicarbonate at a dose sufficient to neutralize endogenous acid improves calcium and phosphorus balance, reduces bone resorption, and increases the rate of bone formation. (N Engl J Med 1994; 330:1776-81.)

THE skeleton is a reservoir of labile calcium that is responsive to humoral mechanisms that maintain the concentration of ionic calcium in extracellular fluid within narrow limits. The skeleton is also a reservoir of labile base (in the form of alkaline salts of calcium) that can be mobilized for the defense of blood pH and plasma bicarbonate concentrations. The role of the skeleton in acid–base homeostasis in adults may contribute to the progressive decline in bone mass that occurs with age, which is ultimately expressed as osteoporosis.[1] The bone loss may result, at least partly, from lifelong mobilization of skeletal calcium salts to balance endogenous acid generated from dietary precursors.[1]

Two conditions must be present for the normal dietary acid load to contribute to the age-related decline in bone mass: a diet-dependent signal for mobilization of the skeletal-base reserve must be continually present, and a fraction of the daily load of endogenous acid must neutralize base from bone and therefore not appear as acid excreted in the urine. Both conditions have been confirmed experimentally. Regarding the first, in subjects eating ordinary diets, blood pH and plasma bicarbonate concentrations are reduced progressively as endogenous acid production is increased within the normal range.[2,3] Reductions in extracellular pH and plasma bicarbonate concentrations are potent and independent signals for the stimulation of bone resorption and inhibition of bone formation.[4-7] With respect to the second, in healthy subjects eating ordinary diets in whom the plasma acid–base composition is stable, net renal acid excretion does not fully account for endogenous acid production.[2,8]

We investigated whether the long-term reduction in the net production of endogenous acid that results from the oral administration of alkali can reduce bone loss. Before initiating long-term studies, we studied postmenopausal women to determine whether reducing the net production of endogenous acid by means of the short-term administration of a particular alkali (potassium bicarbonate for a few weeks) improved calcium and phosphorus balance and reduced bone resorption or increased bone formation.

METHODS

We carried out studies of calcium and phosphorus balance in 18 women who were hospitalized in the General Clinical Research Center of Moffitt–Long Hospitals, San Francisco. The committee on human research approved the protocol, and each woman gave informed consent. The women were white and ranged in age from 51 to 77 years, in weight from 53 to 76 kg, in height from 153 to 175 cm, and in body-mass index (the weight in kilograms divided by the square of the height in meters) from 21 to 28. All had undergone menopause at least five years earlier, were physically active, were taking no medications or hormones, and had normal blood pressure; one was a vegetarian. All were within the expected weight range for their height and frame size according to the method of Weigley[9] and Metropolitan Life Insurance tables for 1983. The bone density of the lumbar spine, measured by computed tomography in 16 women, averaged 94.6 mg per cubic centimeter (range, 47.1 to 144.1). The women's z scores, defined as the number of standard deviations from the average value in a larger group of normal women of the same age studied in the same laboratory, averaged −0.27 (range, −1.6 to +2.1). The bone density of the spine, measured by dual-energy x-ray absorptiometry in nine women, averaged 0.78 mg per square centimeter (range, 0.58 to 0.89), which yielded z scores averaging −1.1 (range, −2.7 to +0.2). Four women had evidence of vertebral compression fractures on radiography.

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The women were given a constant daily diet containing the following mean (±SD) amounts of nutrients per 60 kg of body weight: calcium, 652±180 mg (16±5 mmol); phosphorus, 871±51 mg (28±2 mmol); potassium, 59±3 mmol; sodium, 119±3 mmol; protein, 96±1 g; and energy, 1995±17 kcal. To facilitate adaptation to the diet, each woman's customary calcium intake was taken into consideration in determining her calcium intake (adjusted with calcium carbonate) for the study, and each woman followed the diet for 20 to 22 days before a 6-day control period. After the control period, potassium bicarbonate (60 to 120 mmol per day per 60 kg in aqueous solution) was provided as an alkali supplement for 18 days, then discontinued for a 12-day recovery period, during which dietary intake was otherwise kept constant. We chose potassium rather than sodium bicarbonate because potassium citrate, but not sodium citrate, induced a reduction in urinary calcium concentrations in men with uric acid nephrolithiasis.[10] We hypothesized that in postmenopausal women, the administration of potassium bicarbonate would improve the external mineral balance.

The control periods were six days in length, with pooled stool samples marked with brilliant blue dye. The amount of potassium bicarbonate in stool was determined from the recovery of an ingested nonabsorbable marker (polyethylene glycol).

Sample Collection

Arterialized venous blood samples were collected between 3:30 p.m. and 4:30 p.m., at least three hours 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 five minutes. The frequency of sampling during each of the three study periods (the control, supplementation, and recovery periods) varied, depending on the variable. We analyzed the specimens for blood pH and carbon dioxide tension; plasma total carbon dioxide, sodium, potassium, and chloride levels; and serum creatinine, total calcium, ionized calcium, magnesium, and inorganic phosphorus levels (measured 4 times during the control period, 10 times during the supplementation period, and 7 times during the recovery period); serum 25-hydroxyvitamin D levels (measured once during each period); and serum 1,25-dihydroxyvitamin D, parathyroid hormone, and osteocalcin levels (measured 4, 6, and 3 times).

Each voided urine specimen was divided in half; one half was preserved in acid for measurement of calcium, and the other half was maintained under a thin layer of mineral oil, preserved with thymol, and pooled in 24-hour collections for the determination of pH and carbon dioxide content. In addition, we measured the total volume and the concentrations of ammonium, titratable acid, sodium, potassium, chloride, inorganic phosphorus, magnesium, and creatinine in the 24-hour samples. Hydroxyproline was measured in three, six, and four 24-hour samples from the three periods, respectively.

Because the composition of the diet and the amounts of nutrients ingested by each woman were constant throughout the study, urinary hydroxyproline excretion was not affected by variations in collagen intake; therefore, changes in hydroxyproline excretion were interpreted as indicating changes in the rate of bone resorption.[11-14] Changes in the serum osteocalcin concentration were considered to indicate changes in the rate of bone formation.[13,15-18]

Dietary intake was determined from analyses of duplicate diets.

Laboratory Methods

The methods used for measuring the acid–base, mineral, and electrolyte analytes have been described previously.[2,19] Ionized calcium was measured in heparinized whole blood with a Nova 8 ionized calcium–pH analyzer (Nova Biomedical, Newton, Mass.). Serum osteocalcin and parathyroid hormone were measured by radioimmunoassay and calcitriol by radioreceptor assay, with assay kits obtained from Nichols Institute (San Juan Capistrano, Calif.).

Statistical Analysis

The results were analyzed by repeated-measures analysis of variance of the average values for the three study periods for each woman and post hoc paired comparisons by the Student–Newman–Keuls test, with SAS software. The results are presented as means ±SD.

Results

The calcium balance was negative — that is, more calcium was excreted than ingested — throughout the study, but it was significantly less negative during the period of supplementation with potassium bicarbonate than during the control period ($P = 0.009$) (Table 1). After the discontinuation of potassium bicarbonate supplementation, calcium balance returned toward the more negative values during the control period. The net intestinal absorption of calcium was not significantly influenced by the ingestion of potassium bicarbonate. Rather, the potassium bicarbonate–induced improvement in calcium balance was accounted for by a reduction in urinary calcium excretion (Table 1 and Fig. 1).

The findings with respect to the balance of inorganic phosphorus were qualitatively similar to those for calcium (Table 1 and Fig. 1). The net intestinal absorption of phosphorus was not significantly influenced by potassium bicarbonate supplementation. On a molar basis, the potassium bicarbonate–induced changes in calcium and phosphorus were positively correlated ($r = 0.88$, $P<0.001$).

Table 1. Mineral Balance in 18 Postmenopausal Women before, during, and after the Administration of Potassium Bicarbonate ($KHCO_3$).*

Variable	Before $KHCO_3$ Supplementation	During $KHCO_3$ Supplementation	Change	After $KHCO_3$ Supplementation	Change
Calcium (mg/day/60 kg)					
Intake	652±188	652±188	—	652±188	—
Stool	608±143	616±134	+8±73	592±138	−40±84
Urine	236±86	172±81	−64±19†	224±70	+56±23†
Balance	−180±124	−124±76	+56±76‡	−148±96	−12±88
Phosphorus (mg/day/60 kg)					
Intake	871±51	871±51	—	871±51	—
Stool	419±92	431±87	+9±46	400±82	−31±41‡
Urine	657±59	601±60	−56±42†	657±58	+53±42†
Balance	−208±127	−161±92	+47±64‡	−183±106	−22±43
Potassium (mmol/day/60 kg)					
Intake	59±2	139±30	—	59±2	—
Stool	10±6	12±7	+2±3†	10±6	−2±2†
Urine	48±4	115±27	+66±26†	48±4	−67±26†
Balance	1±7	12±5	+11±4†	1±6	−11±5†
Sodium (mmol/day/60 kg)					
Intake	119±3	119±3	—	119±3	—
Stool	4±3	5±4	+1±2	4±4	−1±4
Urine	106±10	106±14	+0±7	107±13	+1±6
Balance	13±8	12±7	−1±8	12±6	+0±7

*The values are means ±SD. Values in the "Change" columns show the changes from the average for the last six days of the preceding period. To convert calcium values to millimoles per day per 60 kg, divide by 40; to convert phosphorus values to millimoles per day per 60 kg, divide by 31.

†$P<0.001$.

‡$P<0.01$.

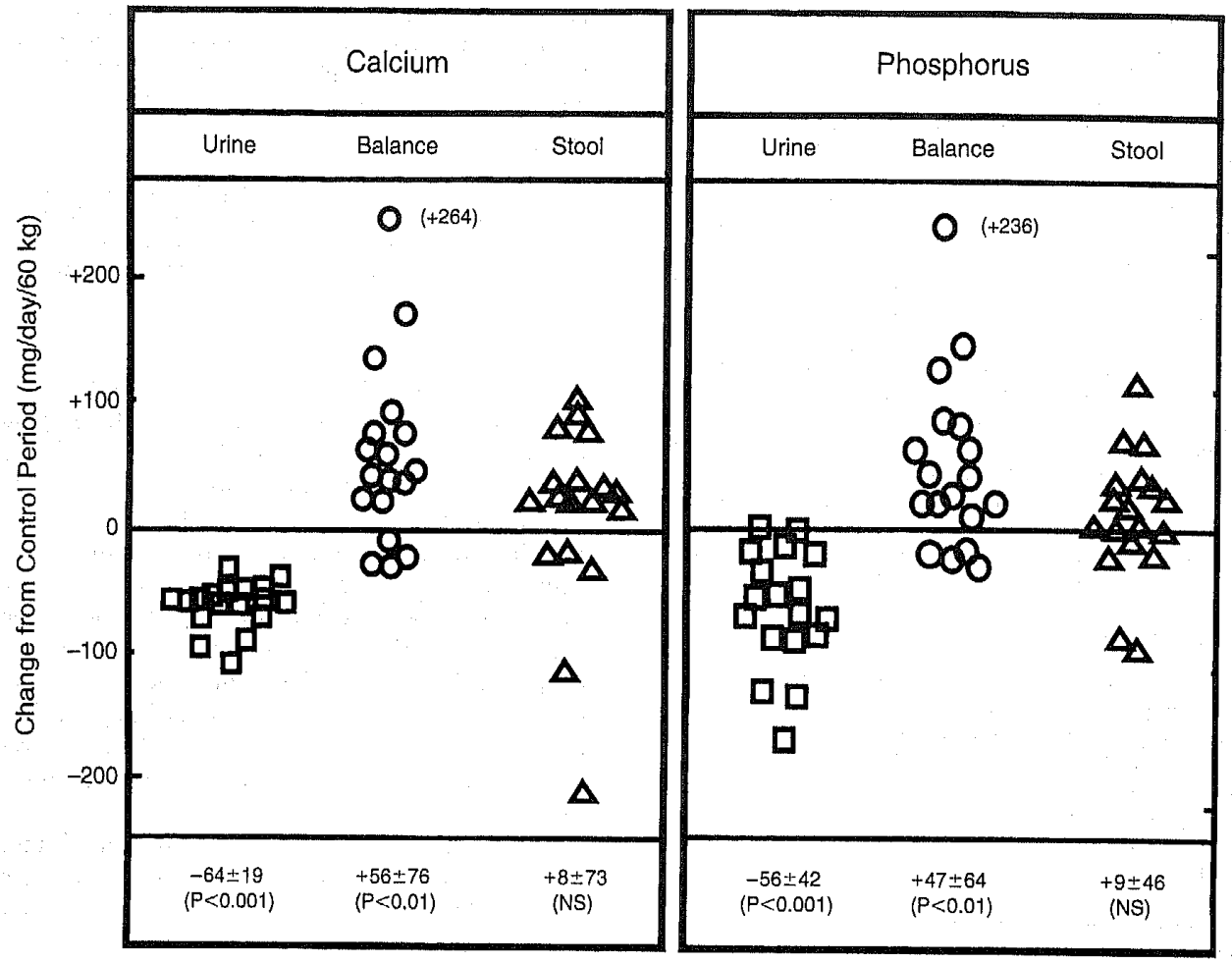

Figure 1. Effect of Potassium Bicarbonate Supplementation on Calcium and Phosphorus Excretion in Urine, External Calcium and Phosphorus Balance, and Calcium and Phosphorus Excretion in Stool in 18 Postmenopausal Women.

The values shown at the bottom of the figure are the average (±SD) potassium bicarbonate–induced changes from the control period (before supplementation). To convert calcium values to millimoles per day per 60 kg, divide by 40; to convert phosphorus values to millimoles per day per 60 kg, divide by 31. NS denotes not significant. The P values are for the comparisons between the control period and the supplementation period.

Potassium balance was nearly zero (neutral) during the control period, became positive during the period of potassium bicarbonate supplementation, and returned to control-period levels after potassium bicarbonate was discontinued (Table 1). The sodium balance was slightly positive throughout the study (Table 1).

Statistically significant and reversible increases in plasma potassium and bicarbonate concentrations and blood pH occurred during the administration of potassium bicarbonate (Table 2). Neither the plasma ionized calcium concentration nor the total inorganic phosphorus concentration changed significantly. The serum 1,25-dihydroxyvitamin D concentration did not change during the period of potassium bicarbonate supplementation, but it increased significantly after supplementation was discontinued ($P<0.001$). Serum parathyroid hormone concentrations increased slightly but significantly ($P = 0.019$) during supplementation; this increase persisted after potassium bicarbonate was discontinued.

The mean serum osteocalcin concentration increased from 5.5±2.8 to 6.1±2.8 ng per milliliter ($P<0.001$) (Table 2), and urinary hydroxyproline excretion decreased from 28.9±12.3 to 26.7±10.8 mg per day (220±94 to 204±82 μmol per day; $P = 0.05$) during potassium bicarbonate administration.

Net renal acid excretion decreased promptly toward zero after the initiation of potassium bicarbonate supplementation (from 70.9±10.1 mmol per day per 60 kg of body weight in the control period to 12.8±21.8 mmol per day per 60 kg during the supplementation period), indicating that endogenous acid was almost completely neutralized during treatment (Fig. 2). After potassium bicarbonate was discontinued, net acid excretion returned promptly to control-period levels (73.2±9.9 meq per day per 60 kg) (Fig. 2).

Discussion

Bone mineral base is released into the systemic circulation when exogenous acid is administered.[3,4,20-22] When acid loading is continued for several weeks or months, excretion of acid in urine — quantitatively the principal component of the homeostatic response to an exogenous acid load — fails to keep pace with the increased load.[20,21] Mobilization of bone alkali continues, bone mineral content and bone mass progressively decline,[23-27] and osteoporosis occurs.[23,24,26-29]

Table 2. Results of Blood Assays in 18 Postmenopausal Women before, during, and after the Administration of Potassium Bicarbonate ($KHCO_3$).*

Index	Before $KHCO_3$ Supplementation	During $KHCO_3$ Supplementation	Change	After $KHCO_3$ Supplementation	Change
Serum					
Total Ca (mg/dl)	9.4±0.17	9.5±0.21	+0.08±0.11†	9.4±0.23	−0.08±0.10†
Ca^{++} (mmol/liter)	4.78±0.15	4.76±0.11	−0.02±0.11	4.80±0.13	+0.06±0.10
Inorganic P (mg/dl)	4.4±0.34	4.4±0.31	+0.02±0.18	4.3±0.33	−0.02±0.17
Mg (mg/dl)	2.1±0.15	2.1±0.11	+0.02±0.08	2.1±0.10	−0.05±0.06‡
Creatinine (mg/dl)	0.73±0.09	0.75±0.09	+0.02±0.03‡	0.73±0.10	−0.03±0.03‡
25-OH-D (ng/ml)	21±8.33	20±7.14	−1.7±3.1‡	18±7.45	−1±3.23
$1,25\text{-}(OH)_2$-D (pg/ml)	38±10.2	37±9.12	−1±3.70	40±10.14	+3±3.51§
PTH (pg/ml)	28±10.28	29±10.19	+2±2.94†	30±10.68	+0±3.65
Osteocalcin (ng/ml)	5.5±2.77	6.1±2.82	+0.6±0.48§	5.7±2.38	−0.4±0.49‡
Albumin (g/dl)	4.3±0.25	4.3±0.20	−0±0.09	4.3±0.19	+0.0±0.10
Plasma (mmol/liter)					
Na^+	140±1.17	140±1.26	−0±0.75	140±1.44	−0±0.85
K^+	3.90±0.15	4.03±0.20	+0.13±0.12§	3.85±0.20	−0.16±0.15§
Cl^-	108±1.41	106±1.21	−2±0.99§	108±1.22	+2±0.83§
HCO_3¶	23.7±1.3	25.6±1.3	+1.8±1.1§	23.4±1.1	−2.09±0.9§
Blood					
pH‖	7.39±0.02	7.41±0.02	+0.02±0.01§	7.40±0.02	−0.02±0.003§

*The values are means ±SD. Values in the "Change" columns show the changes from the average for the last six days of the preceding period. To convert values for calcium (Ca) to millimoles per liter, divide by 4; to convert values for phosphorus (P) to millimoles per liter, divide by 3.1; to convert values for magnesium (Mg) to millimoles per liter, divide by 2.3; to convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for 25-hydroxyvitamin D (25-OH-D) to nanomoles per liter, multiply by 2.496; to convert values for 1,25-dihydroxyvitamin D ($1,25\text{-}OH_2$-D) to picomoles per liter, multiply by 2.4; and to convert values for parathyroid hormone (PTH) to picomoles per liter, multiply by 0.1061. Na denotes sodium, K potassium, Cl chloride, and HCO_3 bicarbonate.

†$P<0.02$.

‡$P<0.01$.

§$P<0.001$.

¶Range: before supplementation, 21.7 to 26.8 mmol per liter; during supplementation, 23.7 to 27.8 mmol per liter; and after supplementation, 21.1 to 25.9 mmol per liter.

‖Range: before supplementation, 7.36 to 7.43; during supplementation, 7.39 to 7.45; and after supplementation, 7.36 to 7.43.

In bone studied in vitro, extracellular acidification increases the activity of osteoclasts, the cells that mediate bone resorption,[7,30-32] and inhibits the activity of osteoblasts, the cells that mediate bone formation.[7]

Lifelong ingestion of ordinary diets constitutes a less intense, more prolonged variant of the short-term experimental administration of large exogenous acid loads. Typical American diets are acid-producing in that renal excretion of acid exceeds excretion of base, and when measured directly, the net balance of endogenous acid (production less excretion) is positive.[3,8] The rate of endogenous acid production is low, however, compared with that induced experimentally with exogenous acid loads. On average, in healthy subjects eating ordinary diets, net renal acid excretion very nearly equals systemic net acid production, hence on average there is no apparent retention of acid that might require, or induce, mobilization of bone mineral base.[3,8] But even with an average value of zero for net acid balance, it is possible that some people have a positive acid balance. Published data indicate that a subgroup of healthy subjects do indeed retain acid in the steady state.[2] Acid balance correlates directly with endogenous acid production.[2] A person will have a positive acid balance if his or her rate of acid production is in the upper half of the normal range, and the balance will more often be positive than negative when acid production is in the mid-normal range.[2]

Thus, even with average rates of endogenous acid production, the kidney fails to keep pace with acid production, with the result that acid is continually retained in the body. Indeed, in normal subjects eating diets that yield rates of endogenous acid production spanning the normal range (0 to 150 mmol per day), we found that steady-state blood acidity was higher and plasma bicarbonate concentrations were lower in direct relation to the steady-state rate of endogenous acid production.[2]

Clearly then, within its normal range, diet-dependent production of endogenous acid can impose an acid load on the body, resulting in both steady-state increases in blood acidity and retention of acid.[2] Although blood pH stabilizes at a progressively lower level with each increasing level of acid production within the normal range, the fact that stability occurs at each level implies a continuing supply of base from an internal reservoir, presumably the skeleton.

If typical acid-producing diets result in a continuing drain on bone mineral base, supplementing the diets with exogenous base might neutralize the acid produced and thereby eliminate the drain on bone. In that case, calcium and phosphorus balance should improve and the rate of bone resorption should decrease. To test that possibility, we measured external calcium and phosphorus balance and urinary hydroxyproline excretion in postmenopausal women who received potassium bicarbonate (60 to 120 mmol per day per 60 kg) as a dietary supplement. The women ate a typical whole-food diet and had a rate of production of en-

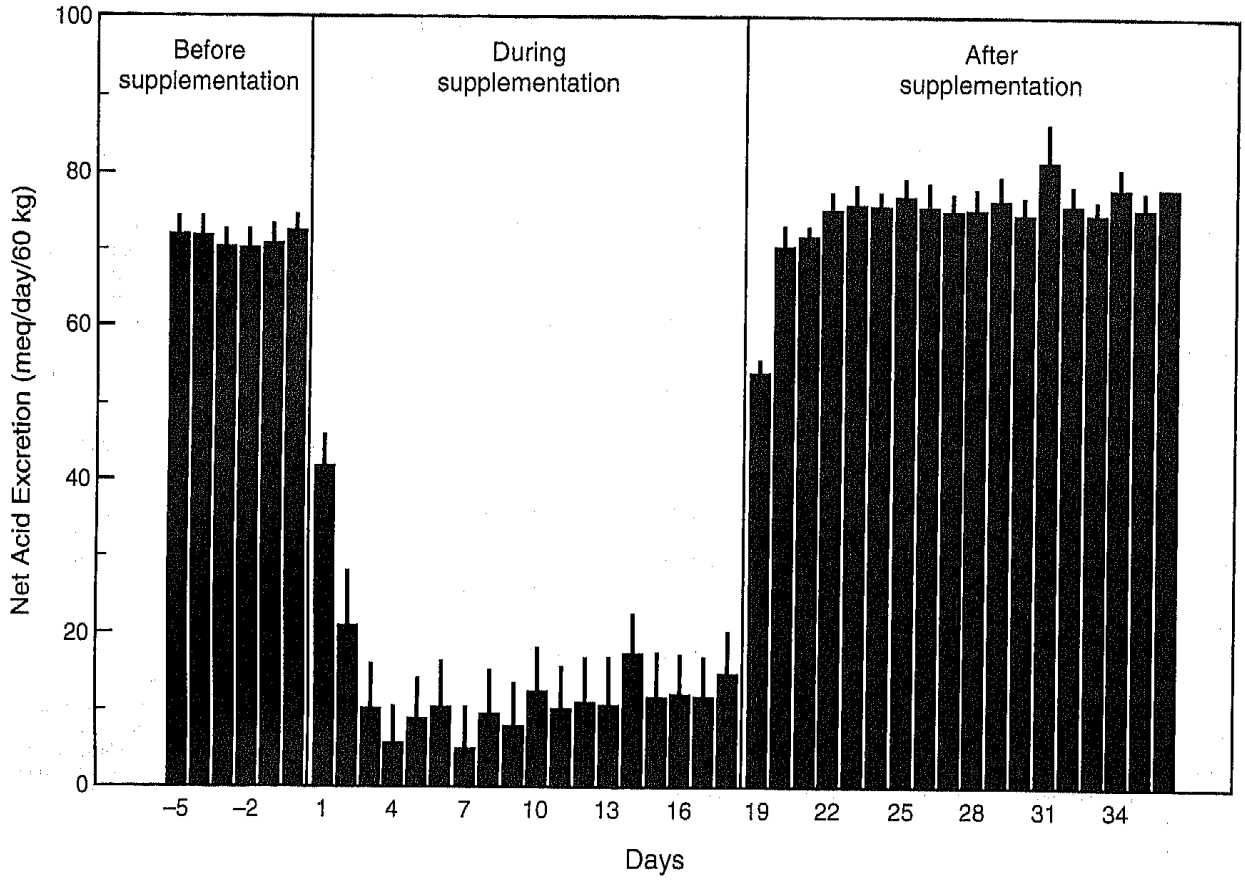

Figure 2. Effect of Potassium Bicarbonate Supplementation on Net Renal Acid Excretion.
The narrow vertical lines above the bars represent 1 SE.

dogenous acid, estimated on the basis of their net acid excretion (50 to 90 mmol per day per 60 kg), that predictably produced a positive acid balance. The administration of potassium bicarbonate induced a significant increase in both the calcium and the phosphorus balance, resulting predominantly from the reduced urinary excretion of these minerals. The improvement in phosphorus balance correlated with an improvement in calcium balance; on a molar basis, the slope of the relation was 1.0, suggesting that one mole of phosphorus was retained per mole of calcium retained. Since the phosphorus:calcium ratio in hydroxyapatite is less than 1.0 (6:10), adequate phosphorus was retained to permit calcium retention as hydroxyapatite. Supplementation with potassium bicarbonate also reduced urinary excretion of hydroxyproline, in association with an increase in the serum osteocalcin concentration. Thus, the administration of potassium bicarbonate appeared to reduce the rate of bone resorption and increase the rate of bone formation.

Taken together, these results suggest that countering the normal diet-related production of endogenous acid with orally administered potassium bicarbonate can attenuate or reverse the loss of bone mass that occurs over the long term in postmenopausal women. Our findings extend those of Lutz[33] that the oral administration of alkali (by means of substitution of sodium bicarbonate for dietary sodium chloride) can improve calcium balance in postmenopausal women, those of Lemann et al.[34] that orally administered potassium bicarbonate (but not sodium bicarbonate) can improve calcium and phosphorus balance in young men, and those of Barzel[35] that orally administered potassium bicarbonate and sodium bicarbonate in combination can attenuate the negative calcium balance induced by immobilization.

Increased plasma acidity or decreased plasma bicarbonate concentrations might stimulate bone resorption directly by favoring the physicochemical process of mineral dissolution and indirectly by reducing the pH and bicarbonate concentration within osteoclasts, thus promoting the adhesion of those cells to their bone-resorptive sites and the secretion of hydrogen ions into the subapical bone-resorbing fluid compartment.[4-7,26,30-32] Acidosis also inhibits osteoblast function,[7] potentially inhibiting bone formation.

Our findings suggest that in postmenopausal women, dietary supplementation with oral potassium bicarbonate in doses sufficient to reduce the net production of endogenous acid reduces the rate of bone resorption, increases the rate of bone formation, and attenuates or reverses the loss of bone in defense of systemic acid–base homeostasis. These findings are consistent with current knowledge of the acid–base responses of osteoclasts and osteoblasts studied in vitro; they suggest that the age-related reduction in bone mass may result at least in part from the cumulative effect of skeletal buffering of diet-dependent

endogenous acid production. The long-term administration of potassium bicarbonate may therefore be effective in preventing and treating postmenopausal osteoporosis.

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