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Perspective

The Skeleton as an Ion Exchange System: Implications for the Role of Acid–Base Imbalance in the Genesis of Osteoporosis

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THE SKELETAL SYSTEM has been aptly described by Green and Kleeman as a giant ion exchange column which is loaded with an alkali buffer.[1] The inorganic crystalline phase of bone contains on its surface a thin layer of permanently adsorbed water which is described as the hydration shell of bone.[2] Eighty percent of body carbonate, 80% of body citrate, and 35% of body sodium are held in solution within this hydration shell. In response to a metabolic acid challenge, the hydration shell of bone can acutely release large amounts of sodium, carbonate, and citrate buffer in an acellular physicochemical reaction.[3,4] In addition, cellular mechanisms actively resorb bone in response to a metabolic acid challenge, providing buffer as a longer term response to the stressed internal milieu.[5–10]

The recognition of the role of bone in the regulation of systemic acid–base balance led to a hypothesis that our diet plays a role in the development of osteoporosis.[11] The daily diet of the average adult American is acid-ash. It is a diet that, upon metabolism (or combustion in the laboratory), generates a residue of approximately 100 mEq of protons, or acid, daily. The endogenous production of protons during the metabolism of neutral food stuff is the result of the conversion of neutral substances such as carbohydrates, fat, or proteins to organic acids or of the oxidation of sulfur-containing amino acids. Organic acids may, in turn, dissociate into organic anions and protons. Sulfur-containing amino acids, such as methionine and cysteine, may be metabolized endogenously to produce CO_2, H_2O, urea, sulfate, and free protons. To the extent that the organic anions or the sulfates are excreted, a residue of protons remains which may have to be buffered. (Skeletal mineralization, the deposition of hydroxyapatite, which can eventually function as an alkali ion-exchange resin, is a source of proton release that may be very significant in premature and rapidly growing infants.)

When confronted by excess protons, or an acid load, the human body employs a number of strategies to maintain normal blood pH. A rapid-response system of limited capacity is that of the bicarbonate/carbonic acid system. Protons combine with bicarbonate to form carbonic acid which dissociates into carbon dioxide and water. This function is controlled by the partial pressure of carbon dioxide and can be modified from minute to minute by changing the rate and depth of respiration. As noted earlier, the majority of the body's carbonate is stored in the hydration shell of the bone crystals and is rapidly available. (A prime pathologic example of this system in action is displayed in patients with diabetic ketoacidosis. When patients with this condition present themselves to the emergency department, they are frequently hyperventilating, their bicarbonate storage is virtually depleted, and the blood bicarbonate level is very low.) A number of renal mechanisms play a prominent part in acid–base metabolism. These include the generation of protons and the acidification of urine, the excretion of titratable acids, and the production of ammonia, which accepts protons and is excreted as ammonium ions. Ammonia production takes a few days to reach its peak, and is therefore important in countering a chronic acid challenge. In such chronic acid loading, there is also a significant contribution of additional buffer from the resorption of bone and the solubilization of hydroxyapatite crystals, which is manifested by increased calciuria.[12,13]

The simplest example of an acid-ash food product is a cola drink. Phosphoric acid is one of the ingredients of such drinks, which have a pH of 3. Since the lowest pH that our kidneys can generate is about 5, we would have to dilute the ingested drink 100-fold to enable urinary excretion of the phosphoric acid, if fully absorbed. That means that a 330 ml can of cola would require nearly 33 l of water for its urinary excretion. The actual amount of fluid required for excretion

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TABLE 1. THE EFFECTS OF CHANGING PROTEIN SOURCE OR QUANTITY ON CALCIUM GI ABSORPTION, URINARY pH, NET ACID AND AMMONIUM EXCRETION, URINARY CALCIUM AND CALCIUM BALANCE

			GI	*Urine*				
Number and ages of subjects	*Diet*	*# of days*	*Calcium absorption (mg/day)*	*pH*	*Net acid (mmol/day)*	*Ammonium (mmol/day)*	*Calcium (mg/day)*	*Calcium (mg/day)*
Breslau et al.[18]								
8 F, 7 M 23–46 years	Vegetarian, soy based	12	0.48 ± 0.04[a]	6.55 ± 0.05	11.9 ± 0.7	22 ± 1	103 ± 15	N.D.
	Ovo-vegetarian	12	0.45 ± 0.03[a]	6.32 ± 0.07	26.0 ± 1.5	28 ± 2	121 ± 12	N.D.
	Animal protein	12	0.45 ± 0.03[a]	6.17 ± 0.07	39.0 ± 1.5 mEq/day	32 ± 3 mEq/day	150 ± 13	N.D.
Schuette et al.[19]								
6 F, 65–79 years 5 M, 44–86 years	F 43 g of protein M 50 g of protein	12	111[b]	N.R.	27.7[b]	15.6[b]	102[b]	8[b]
	F 100 g of protein M 113 g of protein	12	122[b]	N.R.	64.7[b]	42.5[b]	188[b]	−66[b]
Licata et al.[20]								
3 F, 2 M average age 60	0.8 g of protein/kg of body wt	16	110 ± 35	5.7 ± 0.4	N.D.	N.D.	90 ± 17	40 ± 41
	2.0 g of protein/kg of body wt	8–12	107 ± 66	5.1 ± 0.3	N.D.	N.D.	171 ± 22	−64 ± 35

[a] Intestinal ^{47}calcium absorption fraction.
[b] Only individual data and means are reported in this study.
N.R., not reported.
N.D., not done.

is nowhere near this amount, since we buffer the acid and bring it up to pH 5. Since bone is the largest source of buffer in the body, it is likely to participate in the buffering of a cola drink, unless the diet provides adequate buffer.

A study that demonstrates the actual effect of phosphoric acid on calcium metabolism was published by Lau et al.[14] They compared two forms of phosphate therapy for nephrolithiasis. One was K-PHOS©, providing 1 g of elemental phosphorus with 9 mEq of potassium and 23 mEq of sodium as the monobasic salts; the other, Neutra-Phos©, providing 1 g of elemental phosphorous as neutral phosphate with 28 mEq of potassium and 28 mEq of sodium with both monobasic and dibasic forms (ratio 1:3) of phosphate present. The difference in the amount of fixed base (Na + K) between the two preparations, 24 mEq, represented the hydrogen ion load per gram of phosphorus in K-PHOS which required buffering. A 7–10 day regimen comparing 2 g of phosphorus from each of the two preparations, dubbed "acid phosphate" and "neutral phosphate," respectively, showed an increase in titratable acid, ammonium, and net acid excretion, associated with a significant 48 mg/day excess in calciuria in the acid phosphate group ($p < 0.02$). This study demonstrates a principle that tends to be overlooked in calcium balance studies; investigators frequently refer to the total phosphate content of a diet but fail to examine whether it is functionally monobasic, dibasic, or tribasic. Clearly, the actual valence of the phosphate is significant and must be addressed.

The negative effect of increasing animal protein intake on calcium metabolism has been documented in a large number of studies,[15] with few exceptions.[16,17] Three studies that address the effect of varying protein intake on urinary acidity are summarized in Table 1. Breslau et al.[18] studied young people, Schuette et al.[19] studied older volunteers, and Licata et al.[20] studied five osteoporotic patients with an average age of 60. Breslau et al.[18] compared three different diets: one containing 75 g/day of animal protein, one ovo-vegetarian (75 g/day of soy-based vegetable protein with eggs), and the third vegetarian without eggs. Schuette et al.[19] and Licata et al.[20] compared low protein with high protein diets. In all these studies, the dietary calcium, phosphorus, sodium, and potassium content were kept constant between the respective study groups. The gastrointestinal absorption of calcium was not affected by the various diet regimens in any study. The animal protein diet, compared with the vegetarian diet, and the high protein diet, compared with the low protein diet, caused reductions in urinary pH and increases in net acid excretion and in calciuria. All these differences were statistically significant. In the studies by Breslau et al.[18] and by Schuette et al.,[19] urinary calcium excretion was found to be significantly correlated with net acid excretion. The animal protein diet resulted in an increased calciuria of 47 mg/day[18] and a probable decrease in calcium balance. The high protein diets[19,20] caused a significant decrement in calcium balance, as expected.

A simple calculation shows that an uncompensated urinary loss of only 50 mg of calcium per day, if persistent for 20 years, will result in a loss of 365 g of calcium—about half the calcium content of an average young adult female skeleton. What form will such depletion of the skeleton take?

In 1969, Barzel and Jowsey[21] carried out a long-term study in rats, which demonstrated that the chronic ingestion of excess acid selectively increased bone resorption and caused osteoporosis. We also demonstrated that excess acid ingestion aggravated the osteoporosis caused by a low calcium diet. Kraut et al.[22] demonstrated enhanced resorption and osteopenia in response to acid loading in thyroparathyroidectomized rats. Myburgh et al.[23] confirmed and extended the observations that chronic excess acid ingestion causes osteoporosis in rats.

The other side of the coin is the effect of alkali administration on calcium metabolism in people ingesting acid-ash diets. One such study was published by Lutz in 1984.[24] A similar study, in postmenopausal women, was published in 1994 by Sebastian and colleagues.[25] These studies are summarized in Table 2. In Lutz's study,[24] fecal calcium was slightly but not significantly lower on the high protein diets. The effect of $NaHCO_3$ on urinary pH and acid excretion were very significant, the pH being more than 1 U higher in the bicarbonate supplemented group than the high protein group. Calciuria was significantly reduced, and calcium balance was significantly improved with the addition of sodium bicarbonate to the high protein diet. The relationship between urinary net acid excretion and calciuria seemed to approximate that observed by Breslau et al.[18] and Schuette et al.[19] The blood pH and the bicarbonate varied minutely between the groups, but the differences of these variables in this small group were not statistically significant.

In the study by Sebastian et al.,[25] the addition of potassium bicarbonate to a high protein diet did not affect the gastrointestinal absorption of calcium but significantly reduced the net acid excretion and the calciuria, such that the calcium balance became substantially less negative. There were also statistically significant but very small changes, well within the normal range, in blood pH and plasma bicarbonate: the pH was 7.41 ± 0.02 and 7.39 ± 0.02 and the bicarbonate was 25.6 ± 1.3 and 23.7 ± 1.3 mmol/l on the $KHCO_3$ supplemented and on the high protein diet, respectively. Blood osteocalcin, a marker of bone formation, increased significantly with the bicarbonate treatment.

These two studies complement our 1969 rat study.[21] We documented that an equimolar mixture of sodium and potassium bicarbonate stimulated bone production and protected the animals from the osteoporotic effect of a low calcium diet.

It is important to stress that all the studies reviewed here deal with normal physiologic adaptations to a common, if not universal, dietary stress. These and other studies show that only minute changes, well within the normal range, can be detected in the plasma pH and bicarbonate as a result of the ingestion of markedly different diets. Renal net acid excretion and net calcium excretion change significantly, but the latter also remains well within the range that we define clinically as normal. (These observations apply only in part to pathological states such as renal acidosis, whether tubular or uremic, in which the skeletal effects are much more complex.)

TABLE 2. THE EFFECT OF THE ADDITION OF ALKALI TO A HIGH PROTEIN DIET ON CALCIUM ABSORPTION, URINARY ACID PARAMETERS, URINARY CALCIUM EXCRETION, AND CALCIUM BALANCE

			GI		*Urine*				
Number and ages of subjects	*Diet*	*# of days*	*Intake (mg/day)*	*Stool (mg/day)*	*pH*	*Net acid (mEq/day)*	*Ammonium (mEq/day)*	*Calcium (mg/day)*	*Calcium balance*
Lutz[24]									
6 F, 2–40 years	44 g of protein	16	516 ± 2	412 ± 20	6.30 ± 0.1	38 ± 3	26 ± 3	110 ± 6	8 ± 20
4–60 years					6.08 ± 0.06	29 ± 2	17 ± 2	83 ± 4	
2–40 years	102 g of protein	14	515 ± 3	396 ± 19	5.68 ± 0.02	78 ± 3	56 ± 3	171 ± 6	−68 ± 21
4–60 years					5.18 ± 0.06	67 ± 2	41 ± 3	188 ± 10	
2–40 years	102 g of protein +	10	524 ± 4	376 ± 26	7.17 ± 0.06	8 ± 6	26 ± 4	146 ± 6	21 ± 20
4–60 years	70 mEq $NaHCO_3$				6.81 ± 0.06	13 ± 3	18 ± 2	111 ± 10	
Sebastian et al.[25]						mEq/day/60 kg			
18 F, 51–77 years*	96 g of protein/ 60 kg of body wt	18	652 ± 188	608 ± 143	N.R.	70.9 ± 10.1	N.R.	236 ± 86	−180 ± 124
	same + $KHCO_3$ 60–120 mmol/day	18	652 ± 188	616 ± 134	N.R.	12.8 ± 21.8	N.R.	172 ± 81	−124 ± 76
	96 g of protein/ 60 kg of body wt	18	652 ± 188	592 ± 138	N.R.	73.2 ± 9.9	N.R.	224 ± 70	−148 ± 96

* Calcium data expressed as mg/day/60 kg of body wt.
N.R., not reported.

We thus have evidence that an acid-ash diet causes excessive calcium loss and a negative calcium balance and that the ingestion of a carbonate buffer reverses this loss and improves the calcium balance. (Observations on the effect of NH_4Cl and $NaHCO_3$ on calciuria were made as early as 1931.)[26]

It is widely accepted that the premenopausal woman's total calcium intake should be 800 mg. For the postmenopausal woman, whose calcium absorption is poorer,[12,27] a total of 1500 mg of calcium is recommended. In line with this recommendation, calcium carbonate (or a number of other calcium salts) is frequently added to women's intake in amounts expected to bring the total calcium ingested to the recommended level.

Based on the findings and data reported above, I propose that it is not the cation, calcium, but rather the anion, e.g., the carbonate, that is truly the element beneficial to women and may well be beneficial to men as well. It is quite likely that adult and aging persons who take supplemental calcium in the form of calcium carbonate derive a major benefit from the carbonate moiety, which provides buffering for the excess acid of their regular diet and only a moderate benefit from the poorly absorbed calcium. Since the kidney's ability to excrete acid deteriorates with aging,[28] the higher intake of the calcium carbonate by the elderly probably meets their need for a larger supply of buffer.

In conclusion, I reviewed evidence that a high protein diet causes excessive calcium loss due to its acidogenic nature, and that the ingestion of carbonate buffer reverses this excessive loss. It is quite likely that the well-documented age-related loss of bone tissue in both women and men is the result of the habitual ingestion of acid-ash diet in our society. I do recognize that, with one or two exceptions, all the human data thus far available on this subject are the result of short-term studies, 2–3 weeks at most. Our long-term studies in the rat, however, support the hypothesis that the long-term result of acidogenic calcium loss is the development of osteoporosis. A study demonstrating that the incidence of osteoporosis is lower in vegetarians than in omnivores[29] adds credence to this conjecture, as do the demographic studies of Hegsted[30] and Abelow et al.[31] which demonstrate a correlation between animal protein intake in various countries around the globe and hip fracture rates in these countries. Appropriate long-term studies are required in order to verify this hypothesis in man. The most direct way of evaluating this proposition is by prospective studies which will correlate age, bone density, and fracture activity with dietary acid–base intake, urinary acid excretion, and calciuria. A less definitive answer to this research question may be achieved by the correlation of 24 h urinary acid excretion with bone density measurement in population studies.

In the meanwhile, I believe that the recommendation that a woman who eats a "normal" American diet should take supplemental calcium carbonate (or a variety of other calcium salts) has merit: she is likely to benefit whether the beneficial effect is due to the anion's buffering potential or whether it is due to the provision of additional calcium to the skeletal economy. A diet low in animal protein, on the other hand, may prove adequate for preserving the skeleton without any supplements.

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