Assessment Of A Nutrient-Based Approach On Bone Health

J Blum

Citation

J Blum. *Assessment Of A Nutrient-Based Approach On Bone Health*. The Internet Journal of Alternative Medicine. 2006 Volume 4 Number 2.

Abstract

Background: Complementary and alternative medicine use in adults with, or at risk for, osteopenia is common. Although most of the herbs and supplements appear to be fairly safe, there is insufficient evidence that demonstrates their beneficial effects.

Aim of the Study: This study was done to determine whether the current nutrients improve indicators of calcium metabolism and bone status.

Materials and Methods: This human clinical trial was randomized, double-blind, placebo-controlled, and prospective in design. Of a population of 72 individuals who were screened over the telephone, 47 post-menopausal females age 50-75 were included in the study. The enrolled subjects were randomly assigned to receive the active product or placebo, one capsule four times per day for six weeks. The major outcome variables were 24-hour urinary calcium per gram of creatinine, serum Bone Specific Alkaline Phosphatase (BSAP), C-Terminal Telopeptide (CTX), and Osteocalcin (OST).

Results: At the conclusion of the study, subjects who received the active product showed reduction in the 24-hour urinary calcium loss and serum CTX levels. They revealed an increase in BSAP and no change was noted for OST.

Conclusions: Nutrient-based supplementation is able to improve measures of calcium metabolism and bone health in post-menopausal females. Studies of longer duration using endpoints including fracture incidence and bone densitometry should be conducted in the future.

INTRODUCTION

Loss of skeletal calcium is a risk factor for osteoporosis and fractures especially of the spine and proximal femur. As the population ages, this becomes an increasingly prevalent situation. It is the source of excessive morbidity and mortality. In the United States alone there are 10 million individuals with osteoporosis and another 34 million who suffer from low bone density. [1] The majority of therapies are pharmacologically based and often require that the patient must take a medication for decades. These drugs have potentially serious adverse effects and many patients do not respond beneficially. The exact etiology of these conditions of dysfunctional calcium metabolism is not fully understood. The optimal therapeutic approach is not clear either. Hence, it would be desirable to find a nutrient-based approach that can help preserve bone mass with fewer adverse effects.[2,3,4,5,6,7]

Similar to the effects of falling estrogen levels, chronic metabolic acidosis (CMA) has a well-established potential for producing a catabolic effect upon bone. In addition to renal phosphate wasting, experimentally induced CMA also results in hypercalciuria and negative calcium balance attributable to calcium efflux from bone. [8,9,10,11] The modern Western-type diet has been implicated as a cause of life-long mild CMA with secondary bone catabolism caused by the generation of an obligatory daily acid load due largely to endogenous oxidation of cationic and sulfur containing amino acids. [12,13] Although still within the broad range of normal values, plasma bicarbonate concentration decreases progressively when endogenous acid production is increased by dietary changes in normal subjects. [14] CMA directly stimulates the net calcium efflux from bone through both physicochemical and cell-mediated mechanisms.

[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41]

Acidosis has multiple effects on cells, one of which is to increase levels of prostaglandins in a variety of systems.[42,43,44,45] In osteoblasts, prostaglandin production is mediated primarily by cyclooxygenase-2 (COX-2). Elevation of prostaglandin levels, especially PGE2, is associated with calcium egress from bone.

Based upon these observations, a combination of nutrients was formulated that incorporates both alkalinizing properties and COX-2 inhibitory function. It was felt that this product would be safe and might possibly be a useful adjunct in the arena of bone health. To test this hypothesis, a human clinical trial in post-menopausal females was performed.

MATERIAL AND METHODS

STUDY POPULATION

The trial was conducted from August 1, 2006 to January 31, 2007 at the Herbal Research Center in Saco, Maine. From a population of 72 individuals who were solicited via regional advertising, 47 subjects met the inclusion criteria: (1) aged 50-75 years; (2) female; (3) not having osteoporosis; (4) being off calcium and vitamin D supplementation for two weeks; (5) not having taken any drugs that impacted bone metabolism; (6) having otherwise stable health; (7) having passed baseline CMP (comprehensive metabolic panel) testing; (8) having signed informed consent. The protocol was reviewed and approved by the Asentral Human Institutional Review Board (Salisbury, MA). The patients were instructed to maintain an isocaloric diet and their previous eating habits during the study period. All subjects were free to withdraw from the study at any time.

PREPARATION OF SAMPLE AND TREATMENT

The nutrient formulation contained the following ingredients and was manufactured in accordance with generally accepted manufacturing practices at an approved facility in the United States. The formula contained: KHCO3, NaHCO3, MgCO3, Folic Acid, Vitamin D, Vitamin B5, Turmeric, Basil, Sage, Thyme, and Rosemary. The placebo consisted of cellulose and was packaged in capsules of identical size, shape and appearance. All capsules were sealed to prevent odor discrimination. The dose was one capsule four times per day with meals and at bedtime. The subjects were on either arm of the study for six weeks. There was a rolling enrollment process. Subjects were seen and evaluated every two weeks, were screened for adverse effects, questionnaires were administered and compliance was assessed. If more than 10% of the capsules were not taken the subject was deemed non-compliant and was removed from the study.

RANDOMIZATION AND BLINDNESS

All subjects were randomly assigned to one of two groups. The same opaque capsules containing either active product or placebo were administered to the subjects by a research assistant blinded to the contents of the capsules. All subjects were treated in the same fashion.

ASSESSMENT

At baseline and after six weeks of treatment, vital signs, weight, and lab testing were performed. The endpoints consisted of: (1) determination of 24-hour urinary calcium per gram of creatinine; (2) BSAP; (3) CTX; (4) OST. Differences between baseline and off study (week 6) values were computed for all subjects and were compared between those on control and active product. All lab draws were morning fasting specimens or 24-hour urine collections from morning to morning. All lab testing was done using commercially available assays.

STATISTICAL ANALYSIS

The data were analyzed with SPSS software (version 12.0). Paired t tests were used to examine differences between groups at 0 and 6 weeks. All p values were two-tailed, and the * level of significance was set at 0.05.

RESULTS

DEMOGRAPHICS

Tables I and II show the demographic data and clinical profiles at the time of entry into the study. As can be seen, there were no significant differences in the baseline parameters between the two groups. One subject in the control group and one subject in the active product group withdrew for personal reasons. 45 subjects completed the trial.

Figure 1

Table 1: Baseline Characteristics

Parameter	Control	Active	P value
Age (Year)	52.4 ± 6.5	50.9 ± 7.0	0.73
Weight (lb)	180 ± 40.9	198 ± 31	0.22
Height (Inches)	63.3 ± 3.1	64.2 ± 3.1	0.95
BP-S (mmHg)	123 ± 15	123 ± 12	0.37
BP-D (mmHg)	78 ± 11	91 ± 10	0.35
Pulse	77 ± 10	75 ± 10	0.82

Figure 2

Table 2: Medical History (%)

Disorder	Control	Active	P value
Diabetes	8.7	0	0.49
Hypertension	26.2	8.7	0.24
Thyroid	26.1	21.7	1.0
Asthma	8.7	21.7	0.41
COPD	0	0	1.0
Cardiac	4.3	4.3	1.0
Depression	39.1	21.7	0.34
Injuries	21.7	30.4	0.74
Surgeries	78.3	82.6	1.0
Renal Disease	0	0	1.0
Kidney Stones	8.7	4.3	1.0
Gall Bladder Dis	4.3	8.7	1.0
Liver Dis	8.7	8.7	1.0
Gastrointestinal	13	4.3	0.61
Elevated Cholesterol	34.8	47.8	0.55
Cancer	0	8.7	0.49
Osteoarthritis	8.7	4.3	1.0
Rheumatoid	8.7	13	1.0
Neurological Dis	4.3	0	1.0
Migraines	8.7	17.4	0.67
Skin Condition	21.7	30.4	0.74
Diet Restriction	8.7	17.4	0.67
Allergies	60.9	56.5	1.0

BETWEEN-GROUP COMPARISON AT SIX WEEKS

There was no significant difference between groups at six weeks in OST status. Figure I shows a statistically significant (p=0.05) increase in BSAP (1.39 ± 0.47 vs. -0.49 ± 0.88 mcg/L) in the active product group compared to the control group. Figure II shows a statistically significant (p=0.01) fall in CTX (-55.4 ± 23.2 vs. +30.1 ± 23.8 pg/ml) in the active product group. Figure III shows a decrease in urinary calcium/g creatinine (-55 ± 130 vs. +4 ± 53 mg/g) in the active product group (p=0.07).

Figure 3

Figure 1: Change in Bone-Specific Alkaline Phosphatase (BSAP)

	BSAP (mcg/L ± SEM)
Change in Control Group	- 0.49 ± .88
Change in Active Group	+ 1.39 ± .47

(P=0.05)

Figure 4

Figure 2: Change in C-Telopeptide (CTX)

	CTX (pg/ml ± SEM)
Change in Control Group	+ 30.1 ± 23.8
Change in Active Group	- 55.4 ± 23.2

(P=0.01)

Figure 5

Figure 3: Change in 24-Hour Urinary Calcium per gram of Creatinine

	24-hour urinary calcium per gram of creatinine (mg/g +/- SEM)
Change in Control Group	+ 4 +/- 53
Change in Active Group	- 55 +/- 130

(P=0.07)

ADVERSE EFFECTS

No major adverse effects were noted. Three episodes of mild gastrointestinal upset were noted (2-control, 1-active) which were transient and none necessitated withdrawal from the study.

DISCUSSION

This study characterizes the actions of the nutrient combination on metabolic parameters of bone metabolism. Specifically, BSAP increased and CTX diminished. BSAP is a proxy for bone formation, while CTX is one for bone

breakdown. These findings are consistent with a beneficial impact on bone formation and a concurrent decrease in bone breakdown. Since total bone mass is determined by the difference in these indicators, these results suggest a favorable impact on global bone mass.

Examination of evolutionary nutrition provides insight into current aspects of bone health and disease. When analyzed from the perspective of dietary intake and its effect on nutritional acid load, great differences are noted between our "ancestral" diet and current dietary consumption. Day after day, modern food choices expose us to a large acid load throughout our lifetimes. In comparison, Paleolithic diets delivered a neutral, or slightly alkaline, load. [46]

In animal models, CMA results in decreased bone calcium content and gravimetrically determined bone mass, decreased wet tissue femur density, accelerated rates of cortical and trabecular bone resorption, and diminished rates of bone formation. [47,48,49,50,51] In vitro studies have demonstrated that metabolic acidosis is a potent stimulator of bone resorption and inhibitor of bone formation. [52,53] In neonatal mouse calvariae, incubation in acidic media leads to an increase in the level of prostaglandin E2 (PGE2). [43] There is a parallel increase in net calcium efflux and PGE2 levels. The inhibition of PGE2 production by indomethacin strongly limits this acidosis-induced bone calcium release. [54] These results suggest that acid-induced, cell-mediated calcium efflux from bone is regulated, at least in part, by an increase in endogenous PGE2 production.

The nutrient combination was formulated based on the observation that both CMA and prostaglandin synthesis, especially PGE2, act sequentially to produce bone catabolism. Ingredients were selected and combined to interfere with this deleterious metabolic cascade. Support for this concept includes investigation of the effect of alkalinizing therapies on bone function. Using the neonatal mouse calvarial model, alkaline therapy caused a decrease in osteoclastic *-glucuronidase release and an increase in osteoblastic collagen synthesis. The role of prostaglandin synthesis is supported by the results of the Rancho Bernardo study which evaluated the relationship between non-steroidal anti-inflammatory (NSAID) drug use and bone mineral density (BMD). Women who used propionic acid NSAIDs had higher BMD at each of five sites. These results remained significant after controlling for known covariates of osteoporosis. [55]

The components of the nutrient combination include various alkaline salts and herbal COX-2 inhibitors. These were incorporated to increase proton buffering capacity and COX-2 inhibition. A fall in daily urinary calcium losses was observed in the active product group. On a 24 hour basis they lost 59 mg of calcium per gram of creatinine less than the controls. Since the average 24-hour urinary creatinine loss was 1.3 grams, this translates into a daily calcium savings of 77 mg. Metabolic bone loss occurs slowly over decades. If this daily calcium savings is maintained for two decades it would preserve 562 grams of calcium. Since greater than 99% of the calcium resides within the skeleton, this represents almost half the calcium in the skeleton of a healthy young female! That such a savings is possible is suggested by a three year potassium bicarbonate trial that showed no loss of efficacy of the treatment over time. [56]

CONCLUSION

This study demonstrated that supplementation with a combination of herbs, salts and vitamins were able to significantly improve parameters of calcium metabolism and bone health.

References

1. Lane JM, Serota AC, Raphael B. Osteoporosis: Differences and similarities in male and female patients. Orthop Clin N Am 2006;37:601-609.
2. Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. Rheum Dis Clin N Am 2006;32:617-629.
3. Shoback D. Update in osteoporosis and metabolic bone disorders. J Clin Endocrinol Metab 2007;92:747-753.
4. Phillips MB. Risedronate-induced hepatitis. Am J Med 2007;120:e1-e2.
5. Keen R. Osteoporosis: Strategies for prevention and management. Best Pract Res Clin Rheum 2007;21:109-122.
6. Compston J. Treatments for osteoporosis-Looking beyond the horizon. N Engl J Med 2007;356:1878-1880.
7. Yanik B, Turkay C, Atalar H. Hepatotoxicity induced by alendronate therapy. Osteoporosis Int 2007;18:829-831.
8. Lemann J, Litzow JR, Lennon EJ. The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Invest 1966;45:1608-1614.
9. Lemann J, Litzow JR, Lennon EJ. Studies on the mechanism by which chronic metabolic acidosis augments urinary calcium excretion in man. J Clin Invest 1967;46:1318-1328.
10. Bushinsky DA. Net calcium efflux from live bone during chronic metabolic, but not respiratory, acidosis. Am J Physiol Renal Fluid electrolyte Physiol.1989;256:F836-F842.
11. Lemann J Jr, Gray RW, Pleuss JA. Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. Kidney Int 1989;35:688-695.
12. Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. NEJM 1994;330:1776-1781.
13. Wachman A, Bernstein DS. Diet and osteoporosis.

Lancet 1968;1:958-959.
14. Kurtz I, Maher T, Hulter HN, et al. Effect of diet on plasma acid base composition in normal humans. Kidney Int 1983;24:670-680.
15. Maurer M, Riesen W, Muser J, et al. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. Am J Physiol Renal Physiol 2003;284:F32-F40.
16. Bushinsky DA. Metabolic acidosis. In: Jacobson HR, Striker GE, Klahr S, eds. The principles and practice of nephrology. St. Louis: Mosby, 1995:924-925.
17. Bushinsky DA. Internal exchanges of hydrogen ions: bone. In: Seldein DW, Giebisch G, eds. The regulation of acid-base balance. New York: Raven Press, 1989:69-88.
18. Bushinsky DA. The contribution of acidosis to renal osteodystrophy. Kidney Int 1995;47:1816-1832.
19. Bushinsky DA, Krieger NS. Integration of calcium metabolism in the adult. New York: Raven Press, 1992:417-432.
20. Bushinsky DA, Krieger NS. Role of the skeleton in calcium homeostasis. In: Seldin DW, Giebisch G, eds. The kidney: physiology and pathophysiology. New York: Raven Press, 1992:2395-2430.
21. Bushinsky DA, Lam BC, Nespeca R, et al. Decreased bone carbonate content in response to metabolic, but not respiratory, acidosis. Am J Physiol Renal Fluid Electrolyte Physiol 1993;265:F530-F536.
22. Bushinsky DA. Net proton influx into bone during metabolic, but not respiratory, acidosis. Am J Physiol Renal Fluid Electrolyte Physiol 1988;254:F306-F310.
23. Bushinsky DA. Effects of parathyroid hormone on net proton flux from neonatal mouse calvariae. Am J Physiol Renal Fluid Electrolyte Physiol 1987;252:F585-F589.
24. Bushinsky DA, Lechleider RJ. Mechanism of proton-induced calcium release: calcium carbonate dissolution. Am J Physiol Renal Fluid Electrolyte Physiol 1987;253:F998-F1005.
25. Bushinsky DA, Krieger NS, Geisser DI, et al. Effects of pH on bone calcium and proton fluxes in vitro. Am J Physiol Renal Fluid Electrolyte Physiol 1983;245:F204-F209.
26. Bushinsky DA, Levi-Setti R, Coe FL. Ion microprobe determination of bone surface elements: effects of reduced medium pH. Am J Physiol Renal Fluid Electrolyte Physiol 1986;250:F1090-F1097.
27. Bushinsky DA, Wolbach W, Sessler NE, et al. Physicochemical effects of acidosis on bone calcium flux and surface ion composition. J Bone Miner Res 1993;8:93-102.
28. Bushinsky DA, Gavrilov K, Stathopoulis VM, et al. Effects of osteoclastic resorption on bone surface ion composition. Am J Physiol Renal Fluid Electrolyte Physiol 1996;271:C1025-C1031.
29. Bushinsky DA, Gavrilov K, Chabala JM, et al. Effect of metabolic acidosis on potassium content of bone. J Bone Miner Res 1997;12:1664-1671.
30. Bushinsky DA, Goldring JM, Coe FL. Cellular contribution to pH-mediated calcium flux in neonatal mouse calvariae. Am J Physiol Renal Fluid Electrolyte Physiol 1985;248:F785-F789.
31. Bushinsky DA. Net calcium efflux from live bone during chronic metabolic, but not respiratory, acidosis. Am J Physiol Renal Fluid Electrolyte Physiol 1989;256:F836-F842.
32. Chabala JM, Levi-Setti R, Bushinsky DA. Alteration in surface ion composition of cultured bone during metabolic, but not respiratory, acidosis. Am J Physiol Renal Fluid Electrolyte Physiol 1991;261:F76-F84.
33. Bushinsky DA, Sessler NE, Krieger NS. Greater unidirectional calcium efflux from bone during metabolic, compared with respiratory, acidosis. Am J Physiol Renal Fluid Electrolyte Physiol 1992;262:F425-F431.
34. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. Am J Physiol Renal Fluid Electrolyte Physiol 1992;262:F442-F448.
35. Bushinsky DA, Sessler NE. Critical role of bicarbonate in calcium release from bone. Am J Physiol Renal Fluid Electrolyte Physiol 1992;263:F510-F515.
36. Bushinsky DA, Sessler NE, Glena RE, Featherstone GDB. Proton-induced physicochemical calcium release from ceramic apatite disks. J Bone Miner Res 1994;9:213-220.
37. Sprague SM, Krieger NS, Bushinsky DA. Greater inhibition of in vitro bone mineralization with metabolic than respiratory acidosis. Kidney Int 1994;46:1199-1206.
38. Bushinsky DA. Stimulated osteoclastic and suppressed osteoblastic activity in metabolic but not respiratory acidosis. Am J Physiol Cell Physiol 1995;268:C80-C88.
39. Ori Y, Lee SG, Krieger NS, Bushinsky DA. Osteoblastic intracellular pH and calcium in metabolic and respiratory acidosis. Kidney Int 1995;47:1790-1796.
40. Bushinsky DA, Nilsson EL. Additive effects of acidosis and parathyroid hormone on mouse osteoblastic and osteoclastic function. Am J Physiol Cell Physiol 1995;269:C1364-C1370.
41. Bushinsky DA. Metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts. Am J Physiol Renal Fluid Electrolyte Physiol 1996;271:F216-F222.
42. Raisz LG. Physiologic and pathologic roles of prostaglandins and other eicosanoids in bone metabolism. J Nutr 1995;125(Suppl 7):2024S-2027S.
43. Krieger NS, Parker WR, Alexander KM, Bushinsky DA. Prostaglandins regulate acid-induced cell-mediated bone resorption. Am J Physiol Renal Physiol 2000;279:F1077-F1082.
44. Krieger NS, Frick KK, Bushinsky DA. Mechanism of acid-induced bone resorption. Current Opinion in Nephrology and Hypertension 2004;13:423-436.
45. Bushinsky DA, Chabala JM, Gavrilov KL, Levi-Setti R. Effects of in vitro metabolic acidosis on midcortical bone ion composition. Am J Physiol Renal Physiol 1999;277:F813-F819.
46. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005;81:341-354.
47. Barzel US, Jowsey J. The effects of chronic acid and alkali administration on bone turnover in adult rats. Clin Sci (Colch) 1969;36:517-524.
48. Myburgh KH, Noakes TD, Roodt M, Hough FS. Effect of exercise on the development of osteoporosis in adult rats. J Appl Physiol 1989;66:14-19.
49. Delling G, Donath K. Morphometrische, electronenmikroskopische und physikalisch-chemische untersuchungenuber die experimentalle osteoporose bei chronischer acidose. Virchows Arch 1973;358:321-330.
50. Kraut JA, Mishler DR, Singer FR, Goodman WG. The effects of metabolic acidosis on bone formation and resorption in the rat. Kidney Int 1986;30:694-700.
51. Hannan DA. A specific immunoassay for monitoring human bone resorption: quantitation of type I collagen cross-linked N-telopeptides in urine. J Bone Miner Res 1992;7:1251-1258.
52. Bushinsky DA. Stimulated osteoclastic and suppressed osteoblastic activity in metabolic but not respiratory acidosis. Am J Physiol Cell Physiol 1995;268:C80-C88.
53. Krieger NS, Sessler NE, Bushinsky DA. Acidosis

inhibits osteoblastic and stimulates osteoclastic activity in vitro. Am J Physiol Renal Fluid Electrolyte Physiol 1992;262:F442-F448.
54. Carbone LD, Tylavsky FA, Cauley JA, et al. Association between bone mineral density and the use of nonsteroidal anti-inflammatory drugs and aspirin: impact of cyclo-oxygenase selectivity. J Bone Miner Res 2003;18:1795-1802.
55. Morton DJ, Barrett-Connor EL, Schneider DL. Nonsteroidal anti-inflammatory drugs and bone mineral density in older women: the Rancho Bernardo study. J Bone Miner Res 1998;13:1924-1931.
56. Frassetto L, Morris RC Jr, Sebastian A. Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women. J Clin Endocrinol Metab 2005;90:831-834.

Author Information

James M. Blum, Ph.D.
University of New England