

Caffeine, Urinary Calcium, Calcium Metabolism and Bone^{1,2}

LINDA K. MASSEY³ AND SUSAN J. WHITING*

Food Science and Human Nutrition, Washington State University, Spokane, WA 99204-0399 and *Division of Nutrition and Dietetics, College of Pharmacy, University of Saskatchewan, Saskatoon, SA S7N 0W0, Canada

ABSTRACT Oral doses of caffeine increase the urinary excretion of calcium, magnesium, sodium and chloride for at least 3 h after consumption. The hypercalciuric effect can be blocked by adenosine receptor agonists. The effect is proportional to dose per lean body mass and no adaptation to the urinary losses occurs with continuing consumption of caffeine. Uncompensated losses of calcium would be a risk factor for development of osteoporosis. Risks of osteoporosis due to caffeine consumption are reviewed. Comparison of data from epidemiological surveys and animal and human studies suggests that for younger adult women consuming adequate calcium, moderate caffeine intakes may have little or no deleterious effects. Increased urinary and intestinal losses may be compensated for by increased intestinal calcium absorption. However older women do not seem to compensate adequately to maintain their former calcium balance, especially when calcium intakes are below recommendations. *J. Nutr.* 123: 1611-1614, 1993.

INDEXING KEY WORDS:

- caffeine • methylxanthine
- calcium • bone • urine

Caffeine is consumed daily by the majority of individuals in the form of beverages, foods and medications. Caffeine, 1,3,7-methylxanthine, is widely consumed because of its stimulant effects. Caffeine is a weak diuretic (Massey and Wise 1992) and increases sodium and water excretion. In 1982 Heaney and Recker reported that urinary calcium excretion and intestinal calcium secretion were correlated with caffeine consumption in metabolic studies on premenopausal women. The direct action of caffeine to increase urinary calcium excretion has been demonstrated (Massey and Wise 1984). Caffeine also increases urinary excretion of magnesium, sodium, chloride and water, but not potassium, phosphate or creatinine (Massey and Wise 1992). Caffeine-induced urinary loss of calcium is largely attributable to a

reduction in renal reabsorption, because creatinine clearance and filtered load did not change significantly (Bergman et al. 1990). Caffeine's effects are proportional to dose per lean body mass (Massey and Wise 1992). Theophylline, 1,3-methylxanthine, also increases urinary calcium excretion in both rats (Whiting and Whitney 1987) and humans (Colin et al. 1984). Theobromine, a 3,7- methylxanthine found in cocoa products, did not elicit diuresis in rats (Whiting and Whitney 1987) and was considerably less hypercalciuric. Whiting and Hughes (unpublished) found that 1.7 mmol (300 mg) of theobromine in a cocoa-based fudge did not increase human 3-h total urinary calcium volume or sodium excretion compared with consumption of a non-cocoa fudge.

It is now recognized that many of the effects of caffeine are due to adenosine antagonism rather than inhibition of phosphodiesterase as previously hypothesized. Caffeine is structurally similar to adenosine, an extracellular messenger that acts at specific cell surface receptors. Adenosine is produced from adenosine monophosphate when levels of that compound rise due to high cellular energy needs. The most widely recognized role of adenosine in the kidney is as a mediator in the tubuloglomerular feedback response (Osswald et al. 1991). Research in rats suggests antagonism of adenosine receptors is

¹Presented as part of the third Annual Workshop of Nutrition and Bone Health Group given at the Annual Meeting of the American Society for Bone and Mineral Research, October 3, 1992, Minneapolis, MN. Financial support for the workshop was provided by a grant from the National Dairy Council, Rosemont, IL. Guest editor for this supplement was L. K. Massey, Department of Food Science and Human Nutrition, Washington State University, Spokane, WA.

²The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact.

³To whom correspondence should be addressed.

involved in methylxanthine-induced hypercalciuria (McPhee and Whiting 1989). Injection of adenosine or adenosine receptor agonists reduced theophylline-induced hypercalciuria. Similar studies have not yet been conducted in human subjects.

Prostaglandin synthesis has been implicated in methylxanthine-induced hypercalciuria. The role of prostaglandins in calcium excretion itself, however, is controversial (Buck 1983, Rocco et al. 1985). Administering indomethacin, a prostaglandin synthesis inhibitor, to theophylline- or caffeine-fed rats reduces methylxanthine-induced hypercalciuria (Whiting and Whitney 1987). Prostaglandin E₂ (PGE₂) excretion parallels that of calcium excretion in control, sodium- or potassium-fed rats and theophylline plus salt-fed rats (Whiting 1993). In one study of human subjects, aspirin ingestion with or without caffeine was followed by a significant drop in PGE₂ excretion, with a significant correlation between total 3-h PGE₂ and calcium excretion (Whiting 1990). Massey and Hollingbery (1988) found no effect of aspirin given 1 h prior to caffeine. Overall the data suggest that a significant role for prostaglandins in methylxanthine-induced hypercalciuria is unlikely.

Although adaptation to caffeine's well-known stimulant effects occurs with a few days of habitual consumption, no adaptation to caffeine-induced calcium excretion is apparent, either in humans after 1 wk (Massey and Opryszczek 1990) or rats after 3 wk of continued consumption (Whiting and Whitney 1987).

Epidemiological studies on the relationship between caffeine consumption and bone loss or fractures have failed to find an association in younger women. The first reported study by Daniell (1976) found no association of coffee consumption with percent cortical area of the right second metacarpal in 103 white women aged 40–49 y. Neither Picard et al. (1988) nor McCulloch et al. (1990) found associations with caffeine intake in premenopausal women aged 40–50 y or coffee consumption in women aged 20–35 y, respectively. Although Lloyd et al. (1991) reported that caffeine intake had a positive effect on urinary calcium excretion, no association was observed between caffeine intake and bone density in women aged 28–45 y.

In contrast to the studies on young women, about half of the epidemiological studies on older women have found some association between caffeine consumption and bone density. Daniell (1976) reported that although 60–69-y-old women in the lowest tertile of bone mass had a higher incidence of drinking more than four cups of coffee per day (30 vs. 20%), they also had higher frequencies of drinking milk and smoking. Average percent cortical area was similar for higher and lower coffee consumers with similar smoking habits and obesity. Yano et al. (1985) found a significant negative association between caffeine consumption and bone mineral content of the

distal radius and distal ulna in 912 postmenopausal Japanese-American women aged 50–80 y. Mean dietary calcium intake was 10.7 mmol (429 mg) in 670 non-supplement users and 21.6 mmol (865 mg) for the 242 women consuming nutritional supplements, whereas mean caffeine intake was 1.2 mmol (239 mg). Associations were negative but not significant at the proximal radius, proximal ulna and os calcis, suggesting caffeine may have different effects on cortical and trabecular bone. No similar associations were found in males. Weak interactions of calcium intake by quintiles with caffeine intake tertiles in bone mineral content were suggested for women, but not further described. Holbrook et al. (1988) found only a nonsignificant 1.1 relative risk for hip fractures with caffeine consumption of 1.8 mmol/d (352 mg/d) in 957 men and women aged 50–70 y at the start of a 14-y prospective study. From a survey of 5398 college alumnae, Wyshak et al. (1989) found an age-adjusted odds ratio of 2.28 for the association of drinking nonalcoholic carbonated beverages and a first bone fracture at or after age 40 y, but only in former college athletes, not nonathletes. Current coffee or tea drinking or self-restriction of milk was not associated with fracture incidence. Kiel et al. (1990) studying 3170 Framingham Study women (age 50–84 y) in 1971–1974 found that consumption of more than two units of caffeinated beverages (one unit = one cup of coffee or two cups of tea) increased risk of hip fracture by 69%. Coffee and tea consumption was assessed biannually during the 12-y prospective study. Hernandez-Avila et al. (1991) observed a positive relationship between caffeine intake and risk of hip but not forearm fracture in women (age 34–59 y) in a 6-y prospective study. Recently Cooper et al. (1992) reported that overall caffeine consumption was not associated with bone mineral at five of six sites in women aged 40–80 y. Caffeine consumption was associated with improved bone mineral in younger women, but reduced bone mineral in women aged 70–80 y.

A similar differential response by younger vs. older women was seen in the five human metabolic studies. The metabolic studies of Heaney and Recker (1982) found that caffeine consumption was associated with increased urinary calcium excretion and intestinal calcium secretion based on 170 balance studies of premenopausal women (age 35–45 y, mean 42 y). However, when data were adjusted for calcium intake, the association was no longer significant. Calcium absorption was not altered. Predicted calcium balance was -0.1 mmol/d (-6 mg/d) for each 0.9 mmol/d (175 mg/d) increase in caffeine consumption. A follow-up intervention study was then conducted examining 12-d metabolic balances on 16 healthy premenopausal women (average age of 29 y) who were consuming usual intakes of calcium averaging 21.6 mmol (865 mg). In that study (Barger-Lux

et al. 1990), 2.1 mmol (400 mg) of caffeine lowered calcium balance by approximately the amount predicted by equations from the first study, although the effects were not statistically significant. Similarly Smith et al. (1989) found that 1.4 L of diet cola vs. water for 1 wk each had no effect on calcium metabolism except for 24-h cyclic adenosine:monophosphate creatinine ratio. Each of the eight healthy premenopausal women consumed a diet (prepared by the investigators) that contained 20.0 mmol (800 mg) of calcium.

In contrast to the studies in younger women, studies on older women report adverse effects of caffeine on calcium metabolism and bone. We recently completed a study (Massey et al. 1989) in which the subjects were primarily postmenopausal women (mean age 60 y) and were all over 35 y of age. Thirty-seven women abstained from their usual caffeine consumption for 2 wk while maintaining their usual calcium intakes, including supplements. Fasting ultrafilterable calcium increased and serum bone alkaline phosphatase isoenzyme levels decreased only in women consuming <15.0 mmol (600 mg) of calcium daily. Hasling et al. (1992) reported that caffeine intake negatively affected calcium balance in postmenopausal osteoporotic women aged 48–77 y, in contrast to calcium. Dietary factors other than calcium and caffeine were not related to calcium balance in these women.

Several studies on caffeine, bone and calcium metabolism in rats help us interpret these sometimes conflicting results from human studies. The half-life of caffeine in rats is 0.88 h compared with 5.2 h in humans, so dosages must be adjusted to be comparable. When tissue exposure to caffeine is compared using integrated plasma caffeine concentrations, the area under the curve for humans is six times higher than for rats for a given dose per body weight. With this in mind, the apparently high doses given in rat studies are reasonable approximations of human tissue caffeine exposures. Two studies have been reported on caffeine or coffee consumption on bone. Greger and Emery (1987) found that 6.6% instant coffee powder, caffeinated vs. decaffeinated, in a calcium-adequate diet fed to weanling or young anemic rats for 22 d had no deleterious effect on calcium content of bone or four measures of bone strength. Glajchen et al. (1988) reported that chronic caffeine administration for 8 wk to 300-g male rats may slightly increase bone turnover as evidenced by an increase in immunoreactive parathyroid hormone and osteocalcin, although bone histomorphometry was not altered.

Metabolic studies have shown that the kidney and the gastrointestinal system are directly affected by caffeine. Yeh and Aloia (1988) found that feeding 285-g male rats 4% instant coffee for 3 to 4 wk increased not only urinary calcium but also en-

dogenous fecal calcium excretion, causing calcium balance to be significantly reduced. The increased endogenous fecal calcium was due to a 50% stimulation of bile flow, with no change in true absorbed calcium. These results support the human balance data of Heaney and Recker (1982). In contrast, caffeine had no effect on calcium release from calvaria of 6-d-old mice, at either physiological or supraphysiological doses (Bergman et al, 1988). These data suggest that caffeine initially affects calcium metabolism and that effects on bone are secondary to metabolic changes.

An earlier study by Yeh and Aloia (1986) is important for finding patterns in the data described above. Their 1986 study on the effects of caffeine on rats consuming a moderately low calcium diet found that, whereas young rats (4 wk old) increased their 1,25-dihydroxyvitamin D and therefore absorbed more calcium in response to caffeine, older rats (12–13 mo old) did not show this compensating increase. Calcium balance in young rats was unaltered, whereas in older rats it became significantly negative.

Overall the data support the hypothesis that younger women seem to be able to compensate for stresses on calcium metabolism caused by moderate caffeine consumption and are thus less likely to have deleterious consequences to bone than are older women. The age at which this change in adaptability occurs cannot be pinpointed and is likely to be gradual as seen in the data of Cooper et al. (1991). Because no difference in caffeine-induced hypercalciuria is seen with increasing age (Massey and Wise 1992), the failure of adaptation may be in the failure to compensate with increased intestinal absorption, as seen in the study of older rats by Yeh and Aloia (1986). Second, adequate calcium intakes may protect against any negative effects that moderate caffeine intakes may have on calcium metabolism. In the human metabolic studies that have shown no deleterious effects of caffeine, calcium intakes were at least 20.0 mmol (800 mg) (Barger-Lux et al. 1990, Smith et al. 1989). Massey et al. (1989) found that intakes of >15.0 mmol (>600 mg) of calcium daily were not associated with changes in calcium metabolism after caffeine abstinence.

Additional studies are clearly needed on the effects of dietary caffeine on both cortical and trabecular bone in older women at several levels of calcium intake to ascertain the risk to bone of the dietary pattern of high caffeine and low dietary calcium so common to North American women.

LITERATURE CITED

- Barger-Lux, M. J., Heaney, R. P. & Stegman, M. R. (1990) Effect of moderate caffeine intake on the calcium economy of premenopausal women. *Am. J. Clin. Nutr.* 52: 722–725.
- Bergman, E. A., Massey, L. K., Wise, K. J. & Sherrard, D. J. (1990)

- Effect of dietary caffeine on renal handling of minerals in adult women. *Life Sci.* 47: 557-564.
- Bergman, E. A., Newbrey, J. W. & Massey, L. K. (1988) Caffeine does not cause in vitro calcium loss from neonatal mouse calvaria. *Calcif. Tissue Int.* 43: 281-283.
- Buck, A. C. (1983) Renal prostaglandins and calcium excretion in urolithiasis. *J. Intern. Med. Res. Suppl.* 11: 18-23.
- Colin, A. A., Kraiem, Z., Kahana, L. & Hochberg, Z. (1984) Effects of theophylline on urinary excretion of cyclic AMP, calcium and phosphorus in normal subjects. *Miner. Electrolyte Metab.* 10: 359-361.
- Cooper, C., Atkinson, E. J., Wahner, H. W., O'Fallon, W. M., Riggs, B. L., Judd, H. L. & Melton, L. J., III. (1992) Is caffeine consumption a risk factor for osteoporosis? *J. Bone Miner. Res.* 7: 465-471.
- Daniell, H. W. (1976) Osteoporosis of the slender smoker. *Arch. Intern. Med.* 136: 298-304.
- Glaichen, N., Ismail, F., Epstein, S., Jowell, P. S. & Fallon, M. (1988) The effect of chronic caffeine administration on serum markers of bone mineral metabolism and bone histomorphometry in the rat. *Calcif. Tissue Int.* 43: 277-280.
- Greger, J. L. & Emery, S. M. (1987) Mineral metabolism and bone strength of rats fed coffee and decaffeinated coffee. *J. Agric. Food Chem.* 35: 551-556.
- Hasling, C., Søndergaard, K., Charles, P. & Mosekilde, L. (1992) Calcium metabolism in postmenopausal osteoporotic women is determined by dietary calcium and coffee intake. *J. Nutr.* 122: 1119-1126.
- Heaney, R. P. & Recker, R. R. (1982) Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. *J. Lab. Clin. Med.* 99: 46-55.
- Hernandez-Avila, M., Colditz, G. A., Stampfer, M. J., Rosner, B., Speizer, F. E. & Willett, W. C. (1991) Caffeine, moderate alcohol intake, and risk of fractures of the hip and forearm in middle-aged women. *Am. J. Clin. Nutr.* 54: 157-163.
- Holbrook, T. L. & Barrett-Connor, E. & Wingard, D. L. (1988) Dietary calcium and risk of hip fracture: 14-year prospective population study. *Lancet* 2: 1046-1049.
- Kiel, P. et al. (1990) Caffeine and the risk of hip fracture: the Framingham study. *Am. J. Epidemiol.* 132: 675-684.
- Lloyd, T., Schaeffere, J. M., Walker, M. A. & Demers, L.M. (1991) Urinary hormonal concentrations and spinal bone densities of premenopausal vegetarian and nonvegetarian women. *Am. J. Clin. Nutr.* 54: 1005-1010.
- Massey, L. K., Bergman, E. A., Wise, K. J. & Sherrard, D. J. (1989) Dietary caffeine lowers serum ultrafiltrable calcium and raises serum bone alkaline phosphatase in older women consuming low dietary calcium. *J. Bone Miner. Res.* 4(S1): 245 (abs.).
- Massey, L. K. & Hollingbery, P. W. (1988) Acute effects of dietary caffeine and aspirin on urinary mineral excretion in pre- and postmenopausal women. *Nutr. Res.* 8: 845-851.
- Massey, L. K. & Opryszek, A. A. (1990) No effects of adaptation to dietary caffeine on calcium excretion in young women. *Nutr. Res.* 10: 741-747.
- Massey, L. K. & Wise, K. J. (1984) The effect of dietary caffeine on urinary excretion of calcium, magnesium, sodium and potassium in healthy young females. *Nutr. Res.* 4: 43-50.
- Massey, L. K. & Wise, K. J. (1992) Impact of gender and age on urinary water and mineral excretion responses to acute caffeine doses. *Nutr. Res.* 12: 605-612.
- McCulloch, R., Bailey, D. A., Houston, C. S. & Dodd, B. L. (1990) Effects of physical activity, dietary calcium intake and selected lifestyle factors on bone density in young women. *Can. Med. Assoc. J.* 142: 221-227.
- McPhee, M. D. & Whiting, S. J. (1989) The effect of adenosine and adenosine analogues on methylxanthine-induced hypercalciuria in the rat. *Can. J. Physiol. Pharmacol.* 67: 1278-1282.
- Osswald, H., Muhlbauer, B. & Schenk, F. (1991) Adenosine mediates tubuloglomerular feedback response: an element of metabolic control of kidney function. *Kidney Int.* 39 (suppl. 2): S128-S131.
- Picard, D., Ste-Marie, L. G., Coutu, D., Carrier, L., Chartrand, R., Lepage, R., Fugère, P. & D'Amour, P. (1988) Premenopausal bone mineral content relates to height, weight and calcium intake during early adulthood. *Bone Miner.* 4: 299-309.
- Rocco, V. K., Sakhaee, K., Pak, C.Y.C. & Brater, D. C. (1985) Lack of effect of prostaglandins on calcium excretion in normal volunteers. *J. Urol.* 133: 1093-1094.
- Smith, S., Swain, J., Brown, E. M., Wyshak, G., Albright, T., Ravnikar, V. A. & Schiff, I. (1989) A preliminary report of the short-term effect of carbonated beverage consumption on calcium metabolism in normal women. *Arch. Intern. Med.* 149: 2517-2519.
- Whiting, S. J. (1990) Effect of prostaglandin inhibition on caffeine-induced hypercalciuria in healthy women. *J. Nutr. Biochem.* 1: 201-205.
- Whiting, S. J. (1993) Effect of diets high in sodium and potassium on the magnitude of theophylline-induced hypercalciuria in the rat. *Int. J. Vitam. Nutr. Res.* (in press)
- Whiting, S. J. & Whitney, H. L. (1987) Effect of dietary caffeine and theophylline on urinary calcium excretion in the adult rat. *J. Nutr.* 117: 1224-1228.
- Wyshak, G., Frisch, R. E., Albright, T. E., Albright, N. L., Schiff, I. & Witschi, J. (1989) Nonalcoholic carbonated beverage consumption and bone fractures among women former college athletes. *J. Orthop. Res.* 7: 91-99.
- Yano, K., Heilbrun, L. K., Wasnich, R. D., Hankin, J. N. & Vogel, J. M. (1985) The relationship between diet and bone mineral content of multiple skeletal sites in elderly Japanese-American men and women living in Hawaii. *Am. J. Clin. Nutr.* 42: 877-888.
- Yeh, J. K. & Aloia, J. F. (1986) Differential effect of caffeine administration on calcium and vitamin D metabolism in young and adult rats. *J. Bone Miner. Res.* 1: 251-258.
- Yeh, J. K. & Aloia, J. F. (1988) Effect of coffee feeding on the duodenal transport and bile excretion of calcium in the rat. *Nutr. Res.* 8: 1369-1377.