



# Effects of caffeine on bone and the calcium economy

R.P. Heaney\*

Creighton University, 2500 California Plaza, Omaha 68178 Nebraska, USA

## Abstract

Caffeine-containing beverage consumption has been reported to be associated with reduced bone mass and increased fracture risk in some, but not most, observational studies. Human physiological studies and controlled balance studies show a clear but only a very small depressant effect of caffeine itself on intestinal calcium absorption, and no effect on total 24-h urinary calcium excretion. The epidemiologic studies showing a negative effect may be explained in part by an inverse relationship between consumption of milk and caffeine-containing beverages. Low calcium intake is clearly linked to skeletal fragility, and it is likely that a high caffeine intake is often a marker for a low calcium intake. The negative effect of caffeine on calcium absorption is small enough to be fully offset by as little as 1–2 tablespoons of milk. All of the observations implicating caffeine-containing beverages as a risk factor for osteoporosis have been made in populations consuming substantially less than optimal calcium intakes. There is no evidence that caffeine has any harmful effect on bone status or on the calcium economy in individuals who ingest the currently recommended daily allowances of calcium. © 2002 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

Caffeine and the related methyl xanthines are widely distributed in plants throughout the world. All stable indigenous cultures having access to these plant products have developed drinks containing these stimulants. Thus caffeine is probably the most commonly consumed pharmacologically active compound in the world, certainly in Europe and North America. Probably it is partly for that reason that caffeine has often been a target of opportunity for investigators seeking to identify environmental factors that may contribute to the burden of chronic disease. The first publication showing a negative effect of caffeine on the calcium economy came from this author's laboratory (Heaney and Recker, 1982). Shortly thereafter, Massey and colleagues (Massey and Wise, 1984; Massey and Hollingbery, 1988; Bergman et al., 1990) showed that a caffeine-induced diuresis increased urinary calcium loss acutely. On these grounds, caffeine came very quickly to be included in everyone's list of risk factors for osteoporosis. However, later work, summarized in what follows, led to substantial modifications of

the probable importance of caffeine as a contributor to the osteoporosis disease burden.

In this review the possible mechanisms whereby any ingested agent (such as caffeine) may alter bone strength are discussed, and then the evidence that may be available for each with regard to caffeine is examined. The present analysis gives primary weight to investigator-controlled studies such as randomized, controlled trials and physiological experiments under careful metabolic controls, as contrasted with observational studies. Where there are discordances, plausible explanations are offered.

## 2. Mechanisms whereby caffeine might affect bone strength

There are four principal ways an agent may increase fracture risk and/or skeletal fragility (Heaney, 1996): (1) an increase in fall frequency and/or an interference with postural reflexes that protect the body during falls; (2) a reduction of body fat over bony prominences; (3) an interference with the bone remodeling process designed to detect and repair fatigue damage in bone structures; and (4) a decrease in bone tissue mass either globally or in key architectural elements (such as trabecular connections).

There are no recognized data relating caffeine to the first two mechanisms. The third mechanism is itself still inadequately explored for bone generally, and its importance for osteoporotic fractures remains undefined.

*Abbreviations:* ECF, extracellular fluid; PTH, parathyroid hormone

\* Corresponding author. Tel.: +1-402-280-4029; fax: +1-402-280-4751.

*E-mail address:* rheaney@creighton.edu (R.P. Heaney).

However, fatigue damage is a major cause of failure in all engineering structures; it occurs in bone on normal use as well as with sporadic overloading and it is highly likely that it contributes to bony weakness with aging. Its importance in this context is that the consequent fragility need not be associated with a decrease in bone mass. Thus, absence of an effect on calcium balance would not, *ipso facto*, absolve a putative agent from guilt in this context. However, as with falls and padding, there are no studies implicating caffeine in tissue-level surveillance and repair of fatigue damage.

The best studied (but not necessarily the most important) of the causes of skeletal fragility is decrease in bone tissue mass. Such decrease can be brought about either by direct effects on the feedback control system that regulates bone density, or by alteration in the supply of critical minerals (e.g. calcium and phosphorus, but in this context most likely calcium). Most of the available evidence implicating caffeine has focused on possible effects on calcium balance or its integral bone mass. Calcium availability, in turn, can be affected by altering ingested intake, by altering absorption, by altering digestive juice calcium content, or by altering sweat and/or urinary calcium losses. It will be along the lines of this approach (i.e. effects of caffeine that may reduce bone tissue mass) that most of the evidence available in regard to caffeine will be evaluated. However, the other mechanisms are mentioned not just for the sake of completeness, but because they may need to be examined in explaining discordances between conclusions from different types of studies.

### **3. Effects on the calcium economy and on bone tissue mass**

#### *3.1. Experimental studies*

The first published study (Heaney and Recker, 1982) showing an effect of caffeine-containing beverages on the calcium economy in humans was performed on 170 healthy, middle-aged women, and involved careful control of and/or measurement of intakes of calcium, phosphorus, protein and caffeine-containing beverages, and full collections of all excreta under metabolic balance conditions. In multiple regression models, caffeine intake (in the form of tea and coffee consumption) was significantly associated with a slight negative balance effect, amounting to a loss of less than 5 mg of calcium per cup of coffee consumed, or equivalent. There was a suggestion that the caffeine effect might have been exerted through increased urinary calcium and/or through increased endogenous fecal calcium loss. This work was followed shortly by a series of studies by Massey and colleagues (e.g. Massey and Wise, 1984; Massey and Hollingbery, 1988; Bergman et al., 1990), showing that caffeine

induced a significant acute calcium diuresis. However, subsequent studies showed that this renal effect was biphasic (Kynast-Gales and Massey, 1994); that is, the acute increase was followed by a later fall in urinary calcium. While this late fall did not completely obliterate the acute increase reported by the investigators, earlier estimates of the net negative effect of caffeine consumption had to be lowered substantially.

Barger-Lux and Heaney, in two further studies, were able to find no effect at all of caffeine on total 24-h calcium loss. In the first (Barger-Lux et al., 1990), a double-blind, randomized, placebo-controlled, cross-over metabolic balance study, subjects consumed only decaffeinated coffee, but with each cup they also took a capsule containing either caffeine or placebo. No significant difference in calcium balance was found between placebo consumption and 400 mg caffeine/day administered for 19 days. The sample size was small, and the study did not have sufficient power to find a balance effect as small as 5 mg of calcium per cup of coffee, but the urinary calcium component of the balance was sufficiently sensitive to detect a small effect, and here no hint of caffeine-induced calciuria was found. In fact, the mean 24-h urinary calcium was non-significantly greater during the placebo period than during the caffeine period. A similar conclusion was reached in an expanded analysis of the original group of women from this laboratory, now involving over three times as many balance studies as previously, with caffeine consumption once again in the form of tea or coffee. No significant influence of caffeine-containing beverages could be found on either urinary calcium loss (Barger-Lux and Heaney, 1995) or on endogenous fecal calcium loss (Heaney and Recker, 1994). However, the negative balance effect persisted in this analysis, and in the expanded data set was estimated to amount to approximately 4 mg of calcium lost/cup of coffee. In multiple regression modeling, this effect was localized to a slight but significant decrease in calcium absorption efficiency. Calcium intake in these women averaged only about 660 mg/day, or roughly half of current recommendations. (The significance of this point will be discussed further, below.)

Three other human experimental studies have been published. In one, eight premenopausal women were fed a diet containing either 1.4 l diet cola per day (and no other source of caffeine), or an equivalent, caffeine-free beverage for 2 weeks (Smith et al., 1989). No effect was found on 24-h urine calcium. In a second study (Massey et al., 1994), no effect of caffeine consumption was found for total serum calcium, 24-h urine calcium or hydroxyproline excretion in 25 women, both pre- and postmenopause. In the third study (Hasling et al., 1992), calcium balance was measured in 85 women with postmenopausal osteoporosis. In multiple regression models both calcium intake and coffee intake were significantly and independently correlated with balance, the latter

negatively. Although coffee rather than caffeine intake was measured, they calculated a negative balance shift of 6 mg/day for each 100 ml coffee consumed. This is somewhat larger than the 4 mg/cup figure of Barger-Lux and Heaney (1995), who used very similar methods, but in a much larger group of women.

The only other controlled studies of the mechanism of calcium loss with caffeine exposure involved rats fed a high coffee diet. In one (Yeh and Aloia, 1988), rats were fed a diet containing 4% instant coffee by dry weight, in which increases in both digestive juice calcium and urinary calcium were found. The relevance of these data to human coffee consumption is doubtful. In a second study (Sakamoto et al., 2001) using diets with somewhat lower, but still high coffee contents (0.62 and 1.36%), no effect was found at either intake level on indices of bone remodeling or on levels of cytokines implicated in bone resorption.

Thus, the best available human experimental evidence indicates that, in individuals ingesting inadequate calcium intakes, caffeine leads to a small negative calcium balance, through a weak interference with calcium absorption efficiency. The magnitude of the effect is such that it has been estimated that it could be offset by addition of only 1–2 tablespoons of milk to a cup of coffee (Barger-Lux and Heaney, 1995). This conclusion was not tested directly with respect to caffeine, but previous studies had shown that reduced absorption from any cause can be offset by increased calcium intake (Heaney et al., 1975). Moreover, two of the observational studies, discussed further below, found an effect of caffeine-containing beverages only in individuals with low calcium intakes (Barrett-Connor et al., 1994; Harris and Dawson-Hughes, 1994). Hence the bulk of the evidence points to a dependence of the caffeine effect on low calcium intakes.

### 3.2. *Observational studies*

Following the original report of a caffeine effect, and in parallel with the controlled trials and physiological measurements summarized above, associations were sought in observational studies in which bone mass and/or fracture rate were measured and correlated with estimates of caffeine intake developed by asking people about their consumption of caffeine-containing beverages. At least 32 such studies (summarized in Table 1) have been reported in the past several years, involving altogether many thousands of individuals. Seven showed a negative effect of caffeine-containing beverages on the calcium and bone economies, three a partial effect, 21 showed no effect, and two a beneficial effect specifically for tea drinkers.

Four cross-sectional studies (Bauer et al., 1993; Hernandez-Avila et al., 1993; Krahe et al., 1997; Rubin et al., 1999) found a negative association between caffeine

intake and bone mineral density, while 13 similar studies (Hansen et al., 1991; Lacey et al., 1991; Cooper et al., 1992; Johansson et al., 1992; Glynn et al., 1995; Hansen, 1995; Travers-Gustafson et al., 1995; Lloyd et al., 1997; Grainge et al., 1998; Maini et al., 1996; Packard and Recker, 1996; Picard et al., 1988; Hannan et al., 2000) found no significant association. Two additional studies (Barrett-Connor et al., 1994; Harris and Dawson-Hughes, 1994) found an effect, but as noted above, only in individuals consuming low calcium intakes. Five studies evaluated change in bone mineral density; four (Reid et al., 1994; Lloyd et al., 1998; Hannan et al., 2000; Lloyd et al., 2001) found no effect of caffeine and a fifth (Harris and Dawson-Hughes, 1994) reported an effect but, as already noted, only at low calcium intakes. Five case-control studies have been reported, one using osteoporosis as the defining criterion (Blaauw et al., 1994), and four using hip fracture (Nieves et al., 1992; Cumming and Klineberg, 1994; Tavani et al., 1995; Kanis et al., 1999). Only one showed a significant difference in caffeine consumption between cases and controls (Kanis et al., 1999), and that one specifically a lower risk of hip fracture in tea drinkers (but not coffee drinkers).

Finally, four prospective studies evaluated caffeine as one of several risk factors for incident fracture (Kiel et al., 1990; Hernandez-Avila et al., 1991; Cummings et al., 1995; Meyer et al., 1997). All four reported a significant association. In the largest of these studies, utilizing the Framingham cohort, the increase in hip fracture risk was nearly three-fold. However, the highest age in the cohort was 65, and there were few fractures overall. In the Norwegian study (Meyer et al., 1997) fracture risk was increased only for individuals consuming nine or more cups of coffee per day, with no dose–response relationship at lower coffee intakes. In the Study of Fractures (SOF) project cohort (Cummings et al., 1995), the authors were able to identify 17 independent risk factors, caffeine being one of the weaker [odds ratio (OR)=1.2, 95% confidence interval (CI)=1.0–1.5]. In several of these prospective study reports the authors emphasise the uncertainty of the causal connection and note that caffeine-containing beverage consumption may be a marker for other unidentified causal factors (see further below).

The two studies showing a beneficial effect in tea drinkers (Kanis et al., 1999; Hegarty et al., 2000) are difficult to interpret in isolation. Hegarty et al. attributed the benefit to other factors in tea (e.g. flavonoids), but lacking experimental evidence of such an effect, this conclusion can be only speculative. Most of the other studies lumped tea and coffee consumption in their estimates of caffeine intake, and it is not possible specifically to dissect out tea effects from coffee effects. Controlled trials of tea-drinking need to be conducted to resolve these uncertainties.

Table 1  
Observational studies of caffeine effects on bone

Authors	N	Design <sup>a</sup>	Endpoint	Effect	Comment
Barrett-Connor et al. (1994)	980	X	BMD	Yes/No	Neg effect only at <1 serving milk/day
Bauer et al. (1993)	9704	X	BMD	Yes	SOF <sup>b</sup> cohort; one of 12 factors; effect weak
Blaauw et al. (1994)	181	CC	Osteoporosis	No	
Cooper et al. (1992)	298	X	BMD	No?	Neg effect at only one of five bone sites
Cumming and Klineberg (1994)	416	CC	Hip fx.	No	
Cummings et al. (1995)	9516	P	Hip fx.	Yes	SOF <sup>b</sup> cohort; one of 17 factors; 20% inc. in risk
Glynn et al. (1995)	823	X	BMD	No	
Grainge et al. (1998)	580	X	BMD	No	
Hannan et al. (2000)	800	P	Δ BMD	No	Framingham cohort; older subset than in Kiel et al., below
Hansen (1995)	249	X	BMD	No	
Hansen et al. (1991)	121	P	BMD	No	
Harris and Dawson-Hughes (1994)	205	P	Δ BMD	Yes/No	Neg. effect only at Ca intakes <744 mg/day
Hegarty et al. (2000)	1256	X	BMD	Yes	Pos. effect; tea drinkers had higher BMD
Hernandez-Avila et al. (1993)	281	X	BMD	Yes	Weak neg association at one bone site, not others
Hernandez-Avila et al. (1991)	84484	P	Fracture	Yes	Nurses Health Study; 3x increase in hip fx risk prior to age 65 years
Johansson et al. (1992)	619	X	BMD	No	
Kanis et al. (1999)	730	CC	Hip fx	No/Yes	No effect for coffee, small positive effect for tea
Kiel et al. (1990)	3170	P	Fracture	Yes	Framingham subset; risk incr. above 2 cups coffee/day
Krabe et al. (1997)	60	X	BMD	Yes	Neg correlation between caffeine and hip BMD; not spine
Lacey et al. (1991)	178	X	BMD	No	
Lloyd et al. (1997)	138	X	BMD	No	
Lloyd et al. (1998)	81	P	Δ BMD	No	Postmenopausal women
Lloyd et al. (2000)	92	P	Δ BMD	No	Postmenopausal women
Maini et al. (1996)	?	X	BMD	No	
Meyer et al. (1997)	39787	P	Hip fx	Yes	Effect only at 9 or more cups coffee/day
Nieves et al. (1992)	329	CC	Hip fx.	No	
Packard and Recker (1996)	145	P	BMD	No	
Picard et al. (1988)	183	X	BMD	No	
Reid et al. (1994)	122	P	Δ BMD	No	
Rubin et al. (1999)	677	X	BMD	Yes	Neg. correlation between caffeine and hip BMD; not spine
Tavani et al. (1995)	1340	CC	Hip fx.	No	
Travers-Gustafson et al. (1995)	1518	X	BMD	No	

<sup>a</sup> X = cross-sectional; P = prospective; CC = case-control.

<sup>b</sup> Study of fractures.

If these observational studies constituted the only evidence, one would have to conclude that the data were far from consistent or conclusive, and that the effect, found in only a minority of studies, might be spurious. Observational studies, as is generally recognized, cannot establish causality for relationships when detected. By the same token, negative epidemiological studies cannot exclude a relationship. Inevitable errors in estimating exposure both obscure real effects and lead to sometimes complex interactions of the putative independent variables. Usually in epidemiological studies of nutrients, none of the possible responsible factors is directly measured, but is instead estimated from such instruments as, in this instance, food frequency questionnaires. The errors and bias that such methods introduce are immense and have been explored in detail elsewhere (Barrett-Connor, 1991; Heaney, 1991; Heaney, 1997).

One example of a mechanism capable of producing an apparent association is the likely inverse relationship between intake of milk and consumption of caffeine-containing beverages (e.g. Heaney and Recker, 1982;

Barger-Lux and Heaney, 1995). This is both because of the common reciprocity of choices relating to the two beverages, and because total fluid intake is itself less variable than intake of its beverage components. (As one source goes up, others tend to go down.) The effect of calcium intake on bone status, of course, is well established, with more than 50 randomized, controlled trials showing a positive effect of high calcium intake on bone mass, and a negative effect on fracture rate. (See: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, National Academy Press, Washington, DC, 1997 for a summary and analysis of these studies, as well as Heaney, 2000.) Thus, estimates of caffeine intake tend to be inverse surrogates for calcium intake, a factor known to influence bone mass. While not all observational studies have been able to discern this inverse relationship between calcium and caffeine intake (e.g. Kiel et al., 1990), it is likely that intake estimation errors are responsible for this failure. The principal study clearly reporting an inverse association was performed under metabolic balance controls,

where intakes of both caffeine-containing and calcium-containing beverages were measured, rather than estimated.

When a significant association is found, as in the case of caffeine and bone, the purported independent variable may be only a marker for the actually responsible (but sometimes unmeasured) causal factor. Also, whether a factor emerges as significant in various studies depends not just on its actual influence, but on the relative accuracy of the estimates of exposure to the given variable, and all others in the model. Those variables with less estimation error can emerge as significant if they are more precise surrogates for the actual causal factor than are estimates of exposure to that factor itself (Hassager et al., 1991). For example, if caffeine intake is inversely correlated with calcium intake, and if caffeine intake is either estimated more accurately than calcium intake or is more stable over extended periods of time, then caffeine will displace calcium from various stepwise regression models, even if it has no effect in its own right. As estimate accuracy will vary from variable to variable, and from study to study, one can reach no conclusion generally applicable to all epidemiological studies about these matters.

Another illustration, undoubtedly applicable to some extent in the studies summarized here, is the problem of confounding. An example is provided by the study of Johansson et al. (1992) in 619 70-year-old men and women. While a significant bivariate inverse correlation was found between intake of caffeine-containing beverages and bone mass ( $P < 0.01$ ), the relationship disappeared in a multivariate model adjusting for such other factors known adversely to affect bone, such as smoking and physical activity.

Thus, while observational studies can point to possible relationships for testing in stronger designs, they can, themselves, neither establish nor exclude the sought for causal connection. Moreover, in this case, given the evidence of an effect already available from physiological studies, observational studies are redundant today, or at best only confirmatory. As already noted, the observational studies are not the only basis for attributing to caffeine an effect on the calcium economy. Metabolic balance studies do show a weak negative effect of caffeine on calcium absorption, and the most plausible way to harmonize all of the data is to conclude (1) that the effect is real and (2) that the negative preponderance of the observational studies is due to the smallness of the effect size and to the weakness of the methods available for estimating exposure, both to caffeine itself, and to other important covariates.

### 3.3. Dosage considerations

Most of the foregoing studies have used food and beverage table values to estimate caffeine intake. Lloyd

et al. (1997), in directly analysing caffeine content, found that food table values were high by more than 50%. A systematic overestimation of this sort would not affect the correlational analyses described above, but it would influence comparison with dosing studies, such as that of Barger-Lux et al. (1990), who treated subjects with a pharmacologic caffeine preparation in a measured dose of 400 mg/day. This was considered equivalent to an intake of 2–3 cups of brewed coffee per day. If, as Lloyd et al. (1997) suggest, standard coffee contains less caffeine than had been thought, then the study of Barger-Lux et al. (1990) was carried out at an intake equivalent to 3–5 cups of coffee daily. Their conclusion about the absence of an effect on 24-h urinary calcium excretion would thus apply to a higher level of caffeinated beverage consumption than they had thought.

### 3.4. Alternative mechanisms

Caffeine and the other methyl xanthines act in a variety of tissues, generally by interfering with the action of phosphodiesterase and thereby potentiating the activity of agonists acting through the adenylate cyclase–cAMP pathway. At sufficient doses, therefore, they could theoretically exert effects directly on the cellular apparatus controlling bone remodeling. In high enough doses caffeine interferes with fetal rat skeletal development (Nakamoto et al., 1989; Schneider et al., 1990) but has no effect on calcium release from 2-day fetal mouse calvarial cultures (Bergman et al., 1988; Lerner and Mellstrom, 1992). Moreover, very high doses given to adult rats for 8 weeks (equivalent on a body weight basis to 60–70 cups of coffee/day in adult humans) had essentially no effect on bone remodeling, as measured by histomorphometry (Glajchen et al., 1988). Similarly, Sakamoto et al. (2001) found no effect of high-coffee diets on biochemical markers of bone metabolism or on cytokines implicated in bone loss in adult rats. However, Ohta et al. (1999) found slight, but significant reductions in bone strength in ovariectomized adult rats fed very high doses of caffeine (20 mg/kg body weight) for 90 days. Concentrations required to produce direct skeletal effects in animals are higher than experienced by bone in human adult caffeine consumers, and it is unlikely, therefore, that any of the detected effects in humans operate through direct skeletal mechanisms. That was the conclusion reached by Glajchen et al. (1988). However, effective caffeine concentrations can be relatively high at the gut mucosa during absorption from a caffeine-containing meal, and it may be that the observed absorptive interference reflects a direct effect of caffeine (during its own absorption) on the transport system for calcium.

Finally, as noted earlier, an agent affecting propensity to fall, soft tissue padding, or repair of fatigue damage could also explain an increase in skeletal fragility, apart from any effect on the calcium economy itself. While these

effects cannot be excluded, it does not seem necessary to invoke such mechanisms in this setting. Fracture studies and bone mass studies are approximately concordant. Similarly, a sudorific effect of caffeine (increasing sweat calcium losses) could explain a bone mass effect in the absence of measurable changes in absorption or non-dermal outputs. However, such an explanation is also unnecessary, since the physiological studies do show a small effect on absorbed calcium input, probably sufficient to explain the small effects on bone mineral density (BMD).

In brief, the weak effect found on fracture rate in the studies summarized in Table 1 is entirely concordant with the weak effect on bone mass found in the epidemiological studies of Table 1, and both effects are concordant with the weak effect found on the calcium economy in physiological studies.

#### 4. Discussion

Substantial further help in harmonizing the data comes from the observed dependence, in at least two studies, of the effect of caffeine on low calcium intake in the subjects concerned (Barrett-Connor et al., 1994; Harris and Dawson-Hughes, 1994). Because the probable basis for the effect is an interference with calcium absorption efficiency (Barger-Lux and Heaney, 1995), this interaction with calcium intake reveals an important feature of the underlying relationships.

As background, it is useful to recall that calcium ion concentration in the extracellular fluid (ECF) is exquisitely regulated; that is, departures from the reference level are met with hormonal responses designed to correct them. The result is that even large swings in inputs and outputs over the course of a day are associated with only tiny fluctuations in ECF  $[Ca^{2+}]$ . The miniscule decrease in ECF  $[Ca^{2+}]$  produced by an external negative balance of only a few mg/day (the effect size of 3–4 cups of coffee, as estimated by Barger-Lux and Heaney, 1995) would be expected to evoke a small increase in parathyroid hormone (PTH) secretion. PTH, in turn, activates not one, but three effector mechanisms designed to raise ECF  $[Ca^{2+}]$  and to restore it to its prior level. These are: (1) increased synthesis of 1,25(OH)<sub>2</sub> vitamin D (and hence an improvement of absorption efficiency for ingested calcium); (2) increased renal tubular reabsorption of calcium (and hence a reduction of urinary calcium losses); and (3) increased bone resorption, brought about both by direct effect of PTH on the resorptive apparatus and indirectly by enhancement of osteoclastic work efficiency through PTH-induced lowering of ECF phosphate concentration. Internally, ECF  $[Ca^{2+}]$  is returned to the reference level. But the net effect on external calcium balance of these three mechanisms depends entirely on the one unregulated

component of the system, namely the calcium content of the diet.

Manifestly, one and the same increase in 1,25(OH)<sub>2</sub> vitamin D level yields much more calcium from a high than from a low calcium diet. At low calcium intakes, the ECF  $[Ca^{2+}]$  deficit is still satisfactorily offset because the renal and osteoclastic effects of PTH compensate for the decreased absorption potential. Thus ECF  $[Ca^{2+}]$  is maintained (although at a cost to bone). But, at high intakes, for example those in the range of current recommendations (NIH Consensus Conference, 1994; Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, National Academy Press, Washington, DC, 1997), the extra few milligrams needed can be easily extracted from the otherwise large surplus of unabsorbed calcium in ingested food residue. At 1200–1500 mg calcium intakes, extraction of an additional 10 mg means an absorptive increase of only approximately 0.8%, while at a 300 mg intake [approximately the bottom quartile in the several National Health and Nutrition Evaluation Survey studies (Carroll et al., 1983; Alaimo et al., 1994)], the absorptive increase would have to be many times larger—for at least two reasons: (1) because 10 is a larger fraction of 300 mg ingested than of 1200; (2) because at low intakes there is less unabsorbed dietary calcium residue available from which to extract further calcium. Additionally, because absorption is already operating close to its maximal efficiency, there is less capacity to respond to 1,25(OH)<sub>2</sub>D.

It is likely that these quantitative aspects of the regulatory system reflect the high calcium intakes that prevailed during hominid evolution (Eaton and Konner, 1985). In any event, as just noted, the feedback control system, operating to maintain constancy of ECF  $[Ca^{2+}]$  concentration, is “satisfied” when the decrement is offset. There is no known mechanism that “informs” the control system where the needed calcium came from, such as whether from otherwise untapped calcium in the digestate, or from internal stores (bone). In brief, the higher the calcium intake, the more readily will the body adjust to extra demands for calcium, to increased losses, or to absorptive interferences.

#### 5. Comment

James Lind, the Scottish naval surgeon who is credited with eradicating scurvy in the British Navy, noted that onset of symptoms of scurvy was hastened among sailors performing heavy physical work. The solution, of course, was not to decrease the work load of British sailors, but to provide them a source of what would come to be recognized, nearly 200 years later, as an essential nutrient, vitamin C. So, too, with caffeine's exposure of the bone-wasting effect of inadequate calcium

intake: the solution is not to decrease the caffeine intake of the Western world, but to provide adequate sources and intakes of calcium.

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