Calcium supplementation of the diet—II

Not justified by present evidence

Last week we looked at the way diverging views on the role of calcium had arisen. This week we conclude our re-examination of the evidence with a look at the part calcium plays in the menopause, in the elderly, and in fractures.

Skeletal loss at the menopause

There is overwhelming evidence that bone loss in women is associated with gonadal failure at the menopause. In addition, oestrogens prevent bone loss and the risk of subsequent fracture in perimenopausal women.[1-7] The precise action of oestrogens on bone is not, however, certain.

The menopause is associated with increased calcium losses in urine and reduced intestinal absorption of calcium. Low concentrations of calcitriol (1,25-dihydroxyvitamin D_3) have been found by some but not all investigators.[8-10] Heaney *et al*[11 12] have estimated calcium requirements in many middle aged women by balance studies undertaken without large changes in the customary dietary intake of calcium and therefore without the same methodological flaws of earlier work in older women.[13] They found that women with the lower dietary intakes of calcium were in greater negative balance and that there was a positive correlation between calcium intake and balance. Regression analysis showed a mean requirement of greater than 750 mg daily and hence a calculated recommended daily allowance of 1150-1350 mg.[14] These studies in menopausal women show that about three quarters of the women in the United States and Britain, and a far greater proportion throughout the world, have a calcium intake below the computed American allowance.

This interpretation provides a rationale for providing calcium supplements or stimulating its absorption with vitamin D metabolites. It has an intuitive appeal, but the logic is similar to that which might lead doctors to give ground up brains for dementia. The argument also depends critically on whether reduced intestinal absorption of calcium is a cause or a consequence of osteoporosis. Those favouring its causal role argue that oestrogens directly stimulate the production of calcitriol; deficiency at the menopause thus results in deficiency of calcitriol and malabsorption of calcium—thereby aggravating the osteoporotic process. The converse view is that lack of oestrogen induces bone loss and an infusion of the extracellular fluid with calcium. This in turn induces a series of homoeostatic responses that offset the hypercalcaemic challenge of osteoporosis.

These opposing views are difficult to resolve from population studies.[14] If lack of oestrogen induces bone loss then the changes in balance (and apparent requirement) in perimenopausal women are the consequence and not the cause of osteoporosis. The danger of overinterpreting calcium requirements from balance studies is well illustrated by the bone loss of immobilisation, which gives rise to a negative calcium balance; at any given dietary intake the apparent requirement for calcium increases. The conclusion that an increased dietary intake of calcium offsets these losses is clearly misleading and not supported by experimental observation.[15]

Assuming that a low intestinal absorption and negative calcium balance were the consequences of osteoporosis, we would expect that the apparent requirement for calcium would be similar irrespective of the dietary intake. There does seem to be a direct and linear relation between dietary intake and calcium balance in perimenopausal women. The slope of this regression differs from unity and from that of normal subjects—such that women with lower intakes of calcium have the higher apparent requirement.[11 16 17] This observation forms the major thrust of arguments for giving perimenopausal women large amounts of calcium to offset perimenopausal bone loss.[14] The slope describing the relation between calcium intake and apparent calcium requirements is, however, the same in women before and after the menopause (fig 1).[12] This suggests that the menopause is associated with a finite fall in calcium absorption irrespective of dietary intake and argues against calcium deficiency causing perimenopausal bone loss.

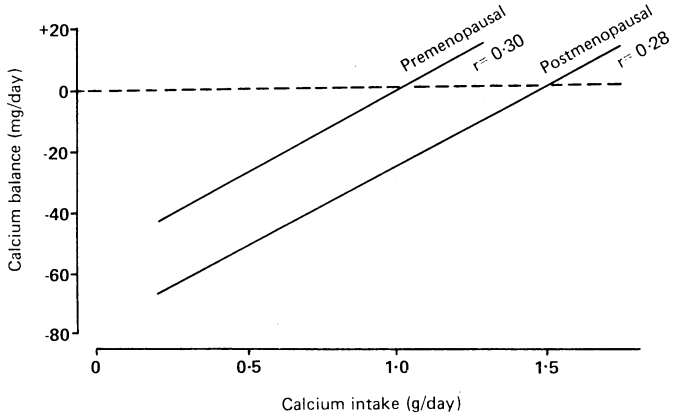

FIG 1—*Relation between external balance and dietary intake of calcium in 207 untreated premenopausal and 41 untreated postmenopausal women (data from Heaney et al*[12])

Ironically the misinterpreted Yugoslavian data discussed last week throws light on this problem as they clearly show that cortical bone loss occurred at an equal rate in both communities—that with a standard intake of calcium and that taking double the amount.[18] Similar conclusions have been made in other large surveys,[19 20] and more recently the rates of cortical and trabecular bone loss at various sites, including the lumbar spine, have been shown to be independent of habitual calcium intake.[21 22]

Even if dietary intake of calcium does not influence bone loss at the menopause large calcium supplements might reduce perimenopausal bone loss. In Denmark 103 women were given a 400 mg calcium supplement to increase their daily intake to 1-2 g.[23] This had no effect on bone loss in the distal forearm over two years. In other well controlled studies large calcium supplements (1500-2000 mg daily) had no measurable effect on trabecular bone loss of the forearm or spine and only small effects at cortical sites.[7 24] In contrast, bone loss was prevented by oestrogens. Increasing the efficiency of calcium absorption with derivatives of vitamin D also has no consistent effect on menopausal bone loss.[5 25]

TABLE I—*Details of controlled studies examining effects of calcium in elderly (not perimenopausal) women*

Study	Age (years)	Years since menopause	Population	No of patients* Enrolled	Completing treatment	Placebo given	Random allocation	Prospective study	Duration (months)	Comments
Horsman *et al*[2]	51	7·0	Healthy women	24	24	No	No	Yes	24	
Recker and Heaney[46]	45-70		Healthy women	16	13	No	Yes	Yes	24	
Recker *et al*[4]	57	7·7	Healthy women	22	22	No	Yes	Yes	24	
Nordin *et al*[45]	64	18·1	Crush fracture	20	20	No	No	Yes	30	Variable duration
Smith *et al*[47]	25-82		"Osteoporosis"	94	94	No	No	No	18-56	Retrospective controls
Albanese *et al*[43]	80		Healthy women	12	12	No	No	Yes	36	
Smith *et al*[48]	80		Healthy women	35	21	Yes	Yes	Yes	36	
Lamke *et al*[44]	60		Colles fracture	20	19	Yes	Yes	Yes	12	

*Women in treated group.

TABLE II—*Results of controlled studies of calcium supplements in elderly (not perimenopausal) women*

Study	Dose (mg/day)	Dietary calcium (mg/day)*	Assessment	Site	Result compared with controls	Significance
Horsman *et al*[2]	800	Not given	SPA	Distal ulna	Decreased loss	p<0·025
			SPA	Distal radius	Decreased loss	NS
			CW	Metacarpals	No difference	
Recker and Heaney[46]	800	1500	Balance†		Improved	NS
			SPA	Distal forearm	No difference	
			CW	Metacarpals	No difference	
Recker *et al*[4]	1040	1543	CW	Metacarpals	No difference	
			SPA	Distal radius	Loss decreased	NS
			XRD	Distal phalanx	Loss decreased	p<0·05
			Kinetic†		Decreased turnover	p<0·01
Nordin *et al*[45]	1200		CW	Metacarpals	Decreased loss	NS
			Balance		Improved	p=0·02
			Fracture	Spine score	Less deterioration	NS
Smith *et al*[47]	1140-1200	Not given	XRD	Metacarpal	Decrease	p<0·01
Albanese *et al*[43]	750	1200	XRD	Second phalanx	Increased density	p<0·001
Smith *et al*[48]	750	Not given	SPA	Proximal third of radius	Gain of bone	p=0·05
Lamke *et al*[44]	800	Not given	XRD	Femoral neck	Increased density	NS
			XRD	Femoral shaft	Increased density	NS

CW=Cortical width; XRD=*x* ray densitometry; SPA=single photon absorptiometry. *With calcium supplements. †After one year.

Further insight into the comparative importance of oestrogens, exercise, and calcium on menopausal bone loss hence comes from studies of bone loss in two groups of young amenorrhoeic women—one being those with anorexia nervosa and the other being marathon runners. Both had reduced skeletal mass, but the runners had more than adequate exercise and an adequate calcium intake.[26 27] This suggests that dietary measures and exercise are not alternatives to oestrogens in maintaining skeletal mass at the time of gonadal failure.

Skeletal losses in the elderly

Bone loss continues throughout later life, but the rate of bone loss falls with advancing years.[19] The questions arise whether calcium intake affects the rate of bone loss in women long past the menopause and whether high intakes may either prevent this loss or rebuild bone. Many studies of calcium requirement have been undertaken in elderly people using balance techniques.[16 28-31] As expected, none showed a mean apparent requirement of less than 800 mg, but none may be interpreted with confidence. Other surveys of elderly people have shown that patients with osteoporosis took less calcium in their diets than those without osteoporosis.[17 28 32 33] One obvious interpretation would be that if such patients had taken more calcium they would have been spared osteoporosis. The alternative view that patients with osteoporosis were smaller or took less exercise and so selected diets of lower energy and calcium content seems not to have been considered. Yet there is no convincing evidence that the rate of bone loss in the elderly varies with dietary intake of calcium, whereas it is modified by exercise.[34] In addition, there is no evidence for a relation between dietary calcium and the incidence of osteoporotic fractures.[35 36] Indeed, hip fractures are less common in populations with low dietary intakes of calcium.[37]

Various problems confound our ability to assess the therapeutic effects of calcium and other agents on the natural course of senile bone loss. Firstly, osteoporosis is a heterogeneous disorder: in some patients the bone loss is predominantly trabecular whereas in others it is cortical.[38] Thus measurements of cortical bone to assess treatment may not reflect changes in trabecular bone. Moreover, there are large differences in the turnover of trabecular tissue at different skeletal sites so that observations made at one site with one technique may not reflect changes at another with the same or different techniques.[39-41]

Many studies have examined the effects of calcium supplements on bone mass or calcium balance in elderly people. Early observers showed that calcium supplements led to positive calcium balance in patients with osteoporosis. It was assumed that this increased skeletal mass and that the avidity of the skeleton was enhanced in this disorder.[16 28 30 42] Therapeutic claims based on these short term balance studies suffer from the same drawbacks as estimates of dietary requirement. Indeed, if acute changes in metabolic balance represented a new steady state then dietary calcium supplements of 1-4 g daily might be expected to increase skeletal mass by more than 10% yearly, a view not consistent with subsequent reports on skeletal mass.

Nevertheless, several controlled studies show that calcium supplements decrease the rate of bone loss in elderly women (tables I and II).[3 5 43-48]

Increases in skeletal mass at regional sites have also been

reported after calcium supplements.[43 48 49] This effect may result from several mechanisms: increased energy consumption[49] or changes induced in remodelling of bone[50] and calcium accretion at quiescent bone surfaces. The suppression of the secretion of parathyroid hormone by large calcium loads should decrease activation of new remodelling sites, but early during treatment bone formation continues at previously existing remodelling sites and bone mass increases transiently. As bone turnover is slow, bone mass may increase transiently for several years before a new steady state is achieved.[41 50] This transient state probably explains why almost no treatment for established osteoporosis has been shown to be ineffective.

Notwithstanding this, if a progressive increase in skeletal mass cannot be attained then at least the rate of loss may be attenuated because new bone formed in the adult is deposited principally at sites of previous resorption. Thus at each remodelling site a finite volume of bone is resorbed (over days) and in patients with osteoporosis a lesser amount is formed (over months). About 6 mmol (250 mg) calcium is resorbed daily and about 5 mmol put back by bone formation at the many remodelling sites. A net daily deficit of 1 mmol calcium is equivalent to a bone loss of about 1% a year. If bone turnover is decreased the number of remodelling sites decreases but the imbalance between formation and resorption at each site persists. Thus if bone turnover is decreased by half bone loss is reduced from 1% to 0·5% yearly. There is good evidence that the turnover of bone decreases in elderly patients given calcium supplements,[4 46] and thus the rate of change of bone mass with therapeutic intervention is unlikely to be linear.

Derivatives of vitamin D that enhance intestinal absorption of calcium have shown fewer consistent effects than calcium supplements alone in elderly patients.[45 51-53] Thus the balance of evidence suggests that diets enriched with calcium do not provide a treatment for osteoporosis by restoring skeletal mass. At best they decrease the rate of bone loss in elderly women rather than in perimenopausal women. This effect is not necessarily negligible as a decrease in the rate of bone loss increases the time taken for a patient to reach a "fracture threshold." The beneficial effects of calcium supplements have, however, been reported mainly in women with advanced osteoporosis who may already have reached a fracture threshold. Furthermore, inhibition of bone turnover may decrease skeletal losses but increase the turnover time of bone and so delay the repair of damage caused by fatigue. Appreciable decreases in bone turnover seem to increase the risk of fracture despite the maintenance of skeletal mass.[41 54] The question thus arises whether the beneficial effects on the rate of bone loss alter fracture frequency.

Effect of calcium on fracture frequency

World wide there is a direct relation between calcium intake and frequency of hip fracture (fig 2). The incidences of fractures of the femoral neck and Colles fractures in Europe are rising at a rate greater than may be accounted for by the aging of the population.[54-58] The cause for these increases are unknown but might be related to changes in energy consumption: in Britain body weights have not changed over the past 20 years but overall food consumption has decreased by about a fifth, suggesting a more sedentary lifestyle. The increase does not seem to depend on calcium intake as the incidence of fractures is increasing equally in Malmö and Oslo, although calcium intake is much higher in Malmö because of its hard water (G Samsioe, personal communication).

As calcium supplements in elderly people decrease bone loss they might be expected to decrease fractures. All postmenopausal women have lost bone but most never suffer from fractures. Thus factors other than the amount of bone convert occult disease into clinically overt osteoporosis.[59 60] For these reasons (and those argued elsewhere[40]) changes in bone mass cannot be reliably interpreted as meaning a corresponding change in the risk of fracture. The therapeutic potential of calcium in the elderly has to be deduced from studies of fracture frequency.

Two studies have reported the beneficial effects of calcium on the frequency of fractures,[45 61] but in both the design of the trial was flawed.[41] Attempts to increase the intestinal availability of calcium with derivatives of vitamin D have not shown a consistently beneficial effect on the frequency of fractures.[51-53 62 63]

Ironically, whether calcium alone prevents fractures may never be answered as, in the United States at least, randomised studies of treating osteoporosis without calcium are now considered to be unethical.[64]

Conclusions

Dietary calcium deficiency is rare in man. Hence arguments about recommended daily allowances are misleading and largely irrelevant for public health. Like Garn,[10] we have come to doubt that adult bone loss is retribution for failing to obtain the recommended daily allowances of calcium. All normal diets contain sufficient calcium, and the excess of calcium present in milk drinkers is not absorbed, which protects them against calcium toxicity.

Despite these considerations calcium supplements might modify the course of disease. Thus in patients with hypoparathyroidism or calcium deficiency accompanying rickets calcium supplements help to restore calcium balance and skeletal metabolism to normal. But the evidence that supplemental calcium increases peak bone mass or decreases the incidence of fractures in elderly people is not convincing. This does not mean that it has no effect, only that an effect has yet to be convincingly shown. Any effect is likely to be small but may not be insignificant: a drug that was only 1% more effective than placebo in reducing the incidence of fractures would prevent more than 1000 fractures a year in Britain. This suggests that even if drugs or dietary manipulations had little efficacy they could still assume considerable importance

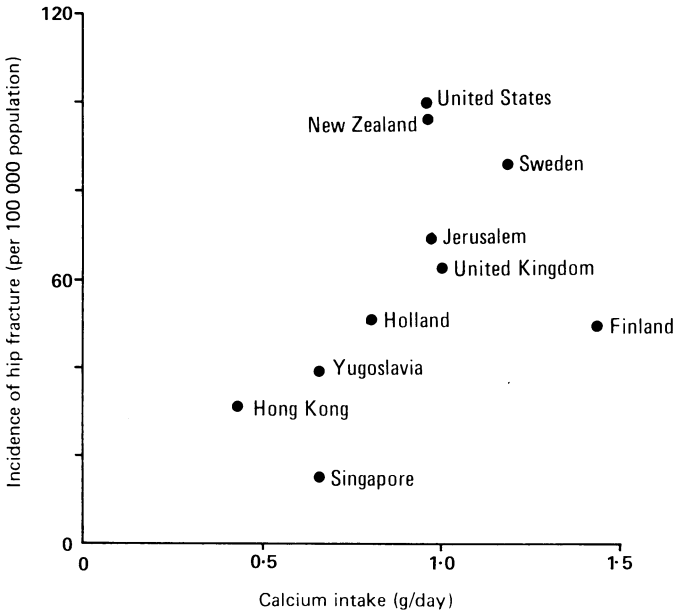

FIG 2—*Relation between age adjusted incidence of hip fracture and dietary intake of calcium in several parts of the world (from Hegsted[57])*

as general health measures. Nevertheless, the argument that, with some exceptions, calcium supplements do little harm and may do some good serves neither the public nor the scientific community when the relative risks and benefits remain undetermined. To healthy citizens who may be worrying about whether their diet has sufficient calcium to meet their needs and whether they should take a supplement we commend Shakespeare's words at the beginning of the first part of this review and advise that they do not need a calcium supplement.

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Richard Packard

In the issue of the *BMJ* of 24-31 December 1988 we published an article entitled "Radiotherapy's second setback: promotion of a potentially dangerous treatment by a back door decision."

In the course of that article it was suggested that Mr Packard had used his influence as the Prime Minister's eye surgeon to have a substantial sum of public money diverted to a form of cancer treatment which we characterised as "a dangerous white elephant."

Mr Richard Packard assures us that he did no such thing and that the decision to allocate £6m of public money towards the installation of a cyclotron at St Thomas's Hospital was made by the ministries concerned following a detailed investigation by them of the merits of cyclotron treatment. We apologise to Mr Packard and the Cyclotron Trust for any suggestion to the contrary.