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Calcium Intake and Body Weight*

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ABSTRACT

Five clinical studies of calcium intake, designed with a primary skeletal end point, were reevaluated to explore associations between calcium intake and body weight. All subjects were women, clustered in three main age groups: 3rd, 5th, and 8th decades. Total sample size was 780. Four of the studies were observational; two were cross-sectional, in which body mass index was regressed against entry level calcium intake; and two were longitudinal, in which change in weight over time was regressed against calcium intake. One study was a double-blind, placebo-controlled, randomized trial of calcium supplementation, in which change in weight during the course of study was evaluated as a function of treatment status. Significant negative associations between calcium intake and weight were found for all three age groups, and the odds ratio for being overweight (body mass index, >26) was 2.25 for young women in the lower half of the calcium intakes of their respective study groups ($P < 0.02$). Relative to placebo, the calcium-treated subjects in the controlled trial exhibited a significant weight loss across nearly 4 yr of observation. Estimates of the relationship indicate that a 1000-mg calcium intake difference is associated with an 8-kg difference in mean body weight and that calcium intake explains ~3% of the variance in body weight. (*J Clin Endocrinol Metab* **85:** 4635–4638, 2000)

McCARRON (1), IN HIS analysis of NHANES-I data, noted an inverse association between calcium intake and body weight. The lack of any plausible basis for connecting these two variables effectively relegated this observation to the status of a curiosity or a chance association. But recently, Zemel *et al.* (2), in an analysis of the NHANES-III database, found a very strong inverse association between relative risk of obesity and calcium intake. Moreover, this observation was not itself an isolated one. Teegarden *et al.* (3), Carruth *et al.* (4), and Skinner *et al.* (5) have recently reported a similar inverse association between body fat gain and calcium intake in children and young women. Now that Zemel *et al.* (2, 6–8) have established a plausible physiological basis for the association, it seemed useful to examine other databases and particularly randomized controlled trials in which calcium supplementation was used for a skeletal end point, to see whether, in a different context, calcium intake was also associated with a weight effect.

Accordingly, we examined the data accumulated in several studies conducted out of our Osteoporosis Research Center over the past 12 yr. Four of these, for their primary skeletal end points, have been published elsewhere (9–12). One is an ongoing randomized trial in which the blind has not been broken, but the entry data were available for cross-sectional analysis.

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Materials and Methods

Subjects

The studies from which our data come are: "YWS" denotes a cohort of 184 healthy women in their early 20s followed for 4 yr (9); "TCD" denotes a similar cohort of young women participants in a randomized controlled trial of calcium supplementation; "Nuns" denotes a prospective study of calcium metabolism and bone health at 5-yr intervals in a cohort of 191 nuns as they passed from premenopause to postmenopause (12); "MBx" denotes a study of bone dynamics and biochemical markers in a cohort of 75 healthy perimenopausal women observed at 6-month intervals over 5 yr (11); and "Van" denotes a randomized controlled trial of calcium supplementation in 216 elderly women (10). The subjects have all been described in greater detail in the respective publications. Table 1 presents the several studies involved, providing relevant information with respect to type of analysis, age group of the subjects concerned, duration of observation, pertinent intake variables, and method of assessing dietary intake. Table 1 also contains the numbers of subjects in each study on whom suitable data were available for this analysis. (For the longitudinal studies we included only women in whom we had at least three observations over time, and we excluded women who, while under study, developed illnesses that might influence weight.) All these projects had been reviewed and approved by Creighton University's Institutional Review Board, and all subjects gave written consent.

Dietary intake assessment

For the nonintervention studies, 7-day food diaries were assessed by registered dietitians using a succession of methods over time. For the Nuns study, beginning in 1967, intakes were assessed using hand calculation, referring to *USDA Handbook 8* and later Bowes and Church (13); computer software was used exclusively in the other four studies and in the Nuns study as it became available. The YWS and MBx studies used NutriPractor (Practorcare, San Diego, CA). Finally, TCD began in 1995 and has used Food Processor (ESHA Research, Salem, OR). For YWS and MBx, both of which had 6-month visit intervals, only the initial diet analysis was used. But for the Nuns study, which had 5-yr visit intervals, the average intake values over the period of observation was used.

Calcium intake was expressed as the calcium to protein ratio, both because this stratagem explicitly factors in the countervailing effects of the two nutrients (13) and because the ratio eliminates most of the portion size estimation error. As we have shown previously (9, 14, 15), the ratio better correlates with an outcome variable known to be asso-

TABLE 1. Characterization of studies incorporated into this report

Study designator	No.	Age (median and range)	Analysis type	Duration of observation (yr)	Outcome variable	BMI (kg/m^2)	Ca intake assessment method	Ca intake (mg/day) (mean ± SD)	Ca:protein (mg/g) (mean ± SD)	Ref.
YWS	150	21 (18–26)	Observational; baseline data	NA	BMI	22.76 ± 3.19	7-day diet diary	784 ± 306	11.78 ± 2.82	9
TCD	198	23 (19–-28)	Observational; baseline data	NA	BMI	22.26 ± 2.865	7-day diet diary	606 ± 185	11.13 ± 2.79	Not yet published
Nuns	146	42 (35–58)	Observational; longitudinal	21.7	Δ Weight	24.00 ± 4.15	7-day diet diary	740 ± 255	10.43 ± 2.69	12
MBx	70	48 (46–54)	Observational; longitudinal	8.47	Δ Weight	25.74 ± 4.65	7-day diet diary	642 ± 304	9.75 ± 2.57	11
Van	216	73 (59–89)	Randomized, controlled trial	3.89	Δ Weight	28.39 ± 4.83	NA	+1200[a]	NA	10

[a] Active treatment group received 1200 mg Ca/day in addition to basal diet Ca.
Ca, Calcium.

ciated with calcium intake (*i.e.* bone gain) than does either nutrient alone, probably for the reasons just cited.

Weight and body mass index (BMI)

Weight and height were measured on entry (as well as at each visit) in virtually all of the studies, using a Harpendon stadiometer for height and either a beam balance or an electronic platform balance for weight. The subjects wore light indoor clothing without shoes. In those subjects without osteoporosis, weight was adjusted for height by using the BMI, expressed as kg/m^2. In older subjects with osteoporosis, in whom height may be spuriously depressed by the disease, weight change during observation or treatment was the outcome variable.

Data analysis

For the cross-sectional data, BMI on entry was regressed against calcium intake on entry, using standard statistical methods, and the slope of the relationship was taken as the outcome variable. For the longitudinal data, weight change was regressed against calcium intake. In the controlled trial, the difference in amounts of weight gained or lost during observation between calcium-supplemented and placebo-treated groups was tested against a null hypothesis of zero difference, using Student's *t* test. Multiple linear regression models were tested using Crunch 4.04 (Crunch Software Corp., Oakland, CA).

Results

Table 2 (*top*) presents the slope values and intercepts for the regression of baseline BMI on dietary calcium to protein ratio (mg/g) for the YWS and TCD studies, together with their 95% confidence limits. The slopes are for BMI (kg/m^2) regressed against dietary calcium to protein ratio (mg/g). The slope was significantly negative for each study. Because the ages, BMI values, and calcium intakes for the two subject groups (TCD and YWS) were similar, we pooled the two datasets to improve the precision of the estimate and present the pertinent statistics for the combination, also in Table 2. The pooled slope was $-0.186\ kg/m^2/mg/g$ ($P = 0.001$). The intercepts in Table 2 represent the predicted mean BMI values for zero calcium intake. These regression relationships were also examined in multivariate models, using combinations of calcium intake, protein intake, energy intake, and finally the computed calcium to protein ratio. Reported energy intake was not correlated with entry weight or BMI, and none of the multivariate models was superior to the simpler bivariate regression of BMI on calcium to protein ratio.

Figure 1 plots the data for the combined set (YWS and TCD). The *horizontal dashed line* in Fig. 1 represents the boundary between normal and overweight, and the *vertical line* represents the median calcium to protein ratio for these 348 subjects. As can be seen, there are substantially fewer subjects in the overweight zone for calcium intakes above than below the median. The odds ratio for being overweight for calcium intakes below the median was 2.25 ($P < 0.02$). The difference was even greater for BMI values greater than 30 (*i.e.* obesity): there were seven obese subjects in the lower half of the calcium intakes and only one in the upper half.

Table 2 (*bottom*) also presents the regression parameters from the two longitudinal observational studies, with, in these studies, change in weight (kg/yr) regressed against dietary calcium to protein ratio (mg/g). In both studies the slope was negative and individually of borderline significance ($0.15 > P > 0.05$). Because the ages, intakes, and weights of the two groups of subjects were similar, we pooled

TABLE 2. Regression parameters measured in the four observational studies (mean and 95% confidence intervals)

Study	Slope (basis and observed values)	Intercept	*P*	r^2
Basal BMI (kg/m^2) on basal CA:protein				
YWS	−0.241 (−0.419,−0.063)	25.59	0.009	0.0453
TCD	−0.167 (−0.309,−0.025)	24.12	0.02	0.0265
YWS + TCD	−0.186 (−0.297,−0.075)	24.60	0.001	0.0304
Weight change (kg/yr) on average Ca:protein				
MBx	−0.053 (−0.111,+0.006)	1.072	0.08	0.0435
Nuns	−0.022 (−0.049,+0.005)	0.545	0.13	0.0179
MBx + Nuns	−0.038 (−0.065, −0.011)	0.781	0.008	0.0319

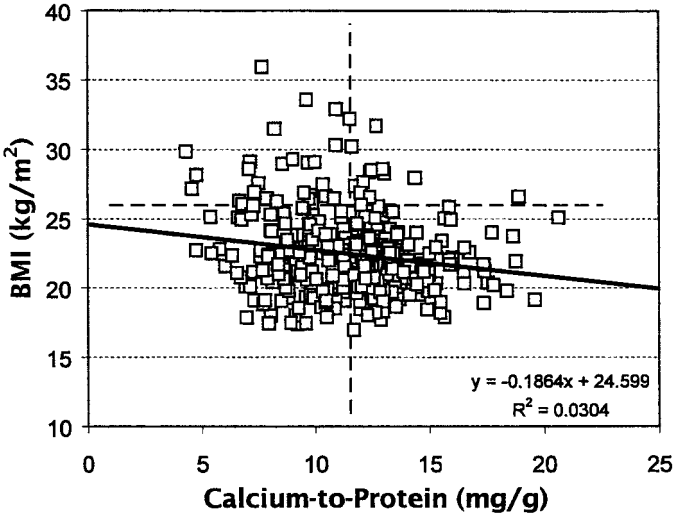

FIG. 1. Plot of baseline BMI values (kg/m^2) against entry calcium to protein ratio (mg/g) in 348 3rd decade women. The *horizontal dashed line* represents the boundary between normal and overweight, and the *vertical line* represents the median intake ratio for these young women. (Copyright 2000, Robert P. Heaney; used with permission.)

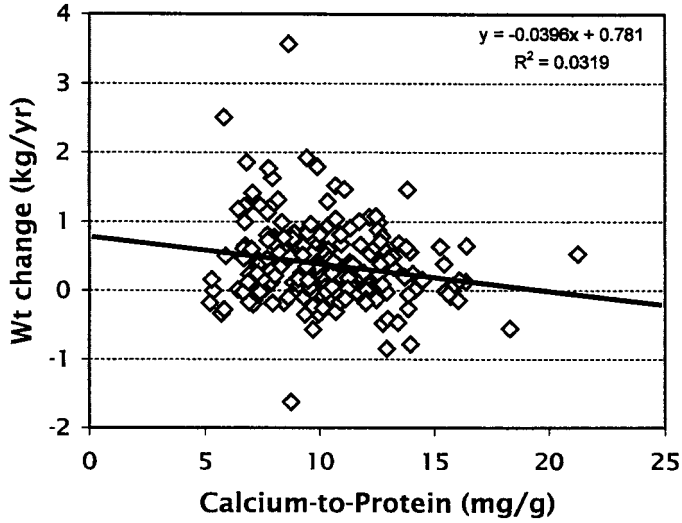

FIG. 2. Plot of weight change (kg/yr) against average calcium to protein ratio (mg/g) in 216 middle-aged women. (Copyright 2000, Robert P. Heaney; used with permission.)

the two datasets (Nuns and MBx), as we had done with the younger women, and recomputed the regression. Table 2 also contains the regression parameters for the combined set, and Fig. 2 presents the data visually. The slope (−0.0383) was highly significantly different from zero ($P = 0.008$). The intercepts represent the predicted value for weight change at mid-life at zero calcium intake. As with the data of the younger women, multivariate models incorporating energy, calcium, and protein intake were not superior to a bivariate model using either the calcium to protein ratio or simply calcium intake alone.

In the Van study (a randomized controlled trial), both groups lost weight over the course of the nearly 4 yr of observation. However, the weight change (± SEM), weighted for duration in study, was −0.671 kg/yr (±0.112) in the calcium-supplemented group, and −0.325 kg/yr (±0.110) in the placebo-control group, for a treatment difference of 0.346 kg/yr ($P < 0.025$).

Discussion

We have shown previously (15) that a low calcium intake tends to be a marker for a poor diet generally. Hence, the associations found in either the young or the middle-aged women do not themselves establish that it was calcium intake that was causal. However, the significant difference in weight loss found in the Van study (a randomized controlled trial) can safely be attributed to calcium. Thus, it is likely that the associations noted in the other four studies are at least partly due to the differences in calcium intake. The consistency of the calcium association across our several studies, together with the concordance of our data with those recently reported by others (2–5), suggests that the effect is real and, we believe, potentially important. However, it should be noted that weight and weight change were not design end points in the studies reported here. Hence, it will be important to perform at least one other controlled trial in which calcium intake is investigator controlled and weight change is the primary outcome variable.

As Table 2 notes, calcium intake in our studies explains ~3% of the variability in weight. There are several likely reasons why this association may be small. Most importantly, body weight is a highly multifactorial variable, and it is unlikely that a very large fraction of its variability could be attributed to any single factor. Also the imprecision of the methods for estimating calcium and protein intakes renders estimates of the independent variable inherently uncertain. With the methods we used (7-day diet diaries and calcium to protein ratios) these errors are less than would be produced by the usual food frequency questionnaire, but they are still not negligible, as we have previously reported (16). Moreover, the intake estimates for the young women were obtained at one point in time, and, for the older women, over a relatively brief portion of their lives, and may well not have been consistent across the years leading up to their contact with us.

The size of the presumed effect can be estimated best by taking apart the calcium to protein ratio and BMI. In the two studies in young women, each 1.0-mg increment in this ratio was associated with a 0.186-kg/m^2 decrement in BMI. For the mean protein intake in these two studies (62.4 g/day), and the mean height (1.66 m), these numbers translate to a predicted 0.82-kg weight decrement for each 100-mg calcium intake increment. And in the middle-aged women, the best estimate of weight change is −0.038 kg/yr/100 mg calcium intake. At a 55% compliance level in the calcium-supplemented group in the Van study (10), the observed difference in weight change translates to −0.052 kg/yr/100 mg calcium intake. This rate of change is of approximately the same magnitude as in the middle-aged women and the difference between them is probably not biologically meaningful.

It may be of interest to note that the predicted weight change in the Nuns and MBx combined cohort (Fig. 2) crosses zero at a calcium to protein ratio of almost exactly 20 mg/g, a figure very close to that derived from current dietary recommendations for both nutrients. Very few women in this age range achieve calcium to protein ratios even close to 20 (see Table 1), and what our data suggest is that the general tendency to gain weight observed in mid life may be due to effectively very low calcium intakes.

Perhaps the largest barrier to prior recognition of a role for calcium intake in body weight has been the lack of a conceptual framework in which to situate the effect or explain its operation, even when it might have been observed. M. B. Zemel (personal communication) has commented that, in his 1990 study of hypertensive blacks (17), he observed substantial weight loss with calcium supplementation but did not report it because it did not seem to fit with what was known either about calcium metabolism or about obesity. However, the same investigator has recently shown that high blood PTH and 1,25(OH)$_2$ vitamin D levels, as would be evoked by a low calcium diet, increase cytosolic [Ca^{2+}] in human adipocytes in culture, switching their metabolism from lipolysis to lipogenesis (2, 6–8). Furthermore, in mice expressing the agouti gene, high calcium diets raised core body temperature and reduced the body fat accumulation that accompanies a baryogenic diet (2, 6). Conversely, low calcium diets resulted in lowered core body temperature and increased fat accumulation.

A plausible background to these phenomena may be found in reflection on the fact that the primitive human diet would have been calcium rich, with calcium to energy ratios two to four times what modern humans ingest (18). High circulating PTH [and correspondingly elevated levels of 1,25(OH)$_2$ vitamin D] would have been experienced only intermittently (*i.e.* at times of food shortage). Because a low calcium intake would have been tantamount to a low food intake, it may be that human physiology used the PTH and 1,25(OH)$_2$ vitamin D response evoked by low calcium intake to regulate its energy metabolism and thereby adapt to imminent food shortage. Today, with calcium intake disconnected from energy intake, the primitive energy-conserving response predisposes to weight gain.

Zemel's mouse model also presents a useful way of thinking about the calcium effect. Briefly, full expression of obesity in the mouse requires a combination of the obesity gene, a baryogenic diet, and low calcium intake. It is likely that some analogous combination is involved in the weight effects observed in humans (*i.e.* ready access to excess energy intake, low calcium intake, a genetic predisposition that impairs adipocyte regulation of cytosolic [Ca^{2+}], and perhaps other factors as well).

It should be noted that, with the exception of the controlled trial, in which calcium carbonate was the calcium source, it cannot be unequivocally determined whether the effect noted in our studies was due to calcium *per se* or to other nutrients for which calcium was a fortuitous marker. The bulk of the calcium in the diets of those with higher intakes was from dairy sources, as would have been expected, and other coingested nutrients may well have been partly responsible for the observed association, as in the DASH study (19). However, calcium itself, presumably through its effect on circulating PTH and 1,25(OH)$_2$ vitamin D, would clearly seem to be involved, as both our controlled human trial and the animal data show. What cannot be excluded at this point is some additional effect produced by other unrecognized dietary elements.

Finally, it may be worth noting the importance of maintaining a high calcium intake during attempts to lose or control weight. The tendency to eliminate milk from many reducing diets may be a partial reason for their frequent failure.

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