Tab E

UNITED STATES DISTRICT COURT DISTRICT OF NEW JERSEY

FEDERAL TRADE COMMISSION, Plaintiff,

v.

LANE LABS-USA, INC., CARTILAGE CONSULTANTS, INC., corporations, and I. WILLIAM LANE and ANDREW J. LANE, individuals

Defendants.

Hon. Dennis M. Cavanaugh

00CV374 (DMC)

DECLARATION OF ROBERT P. HEANEY, M.D.

I, ROBERT P. HEANEY, M.D., DO HEREBY DECLARE PURSUANT TO 28 U.S.C. SEC. 1746, AS FOLLOWS:

I. EDUCATION, EXPERIENCE, AND TRAINING

1. As detailed in my *Curriculum Vitae*, attached hereto as Exhibit 1, I am a physician, with training in Internal Medicine and Endocrinology, and have spent most of my professional life in clinical research, focused primarily around issues of calcium and bone biology, beginning with my work at the National Institutes of Health in 1955.

2. From 1957 to the present I have been employed in various capacities on the faculty of Creighton University in Omaha, Nebraska, first in the Department of Internal Medicine, School of Medicine, then as Vice President for Health Sciences, and most recently (1984 to the present) as John A. Creighton University Professor. I am also a principal in the Osteoporosis Research Center, Creighton University.

3. As set forth in detail in Exhibit 1, I have authored or co-authored 283 peerreviewed publications in the field of clinical investigation, have written or edited four books, including one on design and analysis of clinical investigations for health professionals, have written 129 chapters in major nutrition and bone biology textbooks, and have frequently been asked to contribute editorials to the leading medical journals, including those in the bone, calcium, and vitamin D fields.

4. My research activity has focused largely on defining precisely the metabolism of calcium and the calcium intake requirement, along with developing corresponding information for other nutrients that are necessary for calcium to exert its effects, or which interact with calcium in critical ways. As an instance, my work in mid-life women was the basis for the calcium intake recommendations of the 1984 Consensus Development Conference at the National Institutes of Health on Osteoporosis.

Throughout my investigative career, beginning from my experience at the National Institutes of Health in the 1950s, I have been focused on the use of isotopic calcium tracers as tools to elucidate various aspects of the calcium economy. One application of that approach has been the measurement of calcium absorption, e.g., in

the normal diet, from natural foods, from fortified foods, and from various calcium supplements. Approximately 60 of my publications in peer-reviewed journals reflect the findings of such investigations. Additionally, I have performed dozens of other studies of the absorbability of calcium for various supplement and food manufacturers, the results of which are contained in reports submitted to the commercial entities concerned, but not published formally in the scientific literature.

5. Three examples of my work, pertinent to the present issue, are as follows:

Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. *J Bone Miner Res* 4:469-475, 1989.

Heaney RP, Weaver CM, Fitzsimmons ML. The influence of calcium load on absorption fraction. *J Bone Miner Res* 11(5):1135-1138, 1990.

Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. *Osteoporos Int* 9:19-23, 1999.

In the first of these we defined the calcium absorptive behavior of normal women at mid-life, as a function of dietary calcium intake when studied under steady

state conditions. In the second we defined the acute relationship between calcium load size and the body's ability to absorb it. One general conclusion from both investigations is that, while absorption efficiency falls as calcium load size increases, the total quantity of calcium absorbed nevertheless rises with intake. In the third paper we compared the absorption of calcium carbonate and calcium citrate and found these two principal calcium supplement sources to be absorbed identically. A feature of these (and related) papers has been the defining of these relationships quantitatively.

6. In addition to the research activity described above, and as set forth in Exhibit 1, I served as a member of the Scientific Advisory Committee of the National Osteoporosis Foundation, as a member of its Board of Directors, as the Chairperson of the Study on Osteoporosis for the Office of Technology Assessment (U.S. Congress), and as a member of the Calcium and Related Nutrients Panel of the Food and Nutrition Board of the Institute of Medicine (the body that issued the most recent nutrient intake recommendations for the bone-related nutrients).

7. Also as set forth in Exhibit 1, I have been, or am currently, a member of various professional organizations related to the field of clinical nutrition and bone biology, including the American Society for Bone and Mineral Research, the International Bone and Mineral Society, the Endocrine Society, the American Society for Clinical Nutrition, and the American College of Nutrition. I am also a

fellow of the American College of Physicians. Additionally, I have been given honorary membership in the American Dietetic Association. Some of these organizations have honored me with various awards, including Fellowship in the American Institute of Nutrition, the McCollum Award of the American Society for Clinical Nutrition, the E.V. McCollum International Lectureship for the American Society for Nutritional Sciences, and the Frederic C. Bartter Award for clinical investigation of the American Society for Bone and Mineral Research.

8. I can recall two principal legal actions, relevant to the current issue, in which I served as a testifying expert. One was an action of the FTC (1996) against a supplement manufacturer, Metagenics, Inc., on whose behalf I served as an expert witness, and the other was a trial in federal court in New York City litigating a dispute between two supplement manufacturers. Additionally, in quasi-legal actions, I have several times served as an expert witness for one or the other of contending parties in actions before the National Advertising Division of the Better Business Bureau. To the best of my recollection all of these actions involved claims related to calcium absorbability from particular supplements, and the effects of the absorbed calcium on bone.

II. BACKGROUND CONSIDERATIONS

9. A high calcium intake reduces the risk of developing osteoporosis and is an essential component of its treatment. This conclusion has been reached by at least three NIH Consensus Development Conferences, by the FDA in its permitted health claims, by the Food and Nutrition Board of the Institute of Medicine in its Dietary Reference Intakes (1997), by the Surgeon General in his 2004 Report on Bone Health, and by the 2005 Dietary Guidelines for Americans. This much is not in contention.

Calcium, from any source, once ingested, needs to be absorbed into the blood stream. ("Absorption" here means transport from the interior of the intestine into the blood.) Absorption efficiency for calcium is low. What is not absorbed stays in the gut and is ultimately eliminated in the feces. Gross absorption for typical meal sizes and loads averages about 25–35%, and net absorption is generally in the range of 10-15%. (The distinction is based on the fact that, in addition to *leaving* the gut, calcium is also *entering* the gut in digestive secretions and sloughed-off mucosa.)

10. Unabsorbed calcium exhibits important functionality in its own right, but for prevention and treatment of disorders such as osteoporosis, it is the *absorbed* calcium that is functionally important.

11. Once absorbed, calcium loses its source identity, as the other components of the salt itself (and of its formulation as a supplement) are handled separately by the body.

12. For the same amount of calcium absorbed, all calcium salts and supplements produce approximately the same effect, i.e., they share in the generic benefit of calcium, *per se* (see above).

13. Different brands/formulations of the same calcium salt (same in the sense of chemical identity) commonly exhibit substantially different absorbabilities. The basis for these differences is not well characterized, but, from experience with pharmacologic agents, is probably due to effects of the so-called "inert" ingredients. I have performed research in my laboratory at Creighton establishing at least a twofold difference between the least and the best absorbed formulations of the most commonly consumed salt, calcium carbonate. However, even a less well absorbed product can confer nutritional benefit so long as some of its calcium is absorbed.

14. Absorbability (bioavailability) of calcium is measured by tracer-based methods, by pharmacokinetic methods, and by pharmacodynamic methods.

7

The tracer-based are the most precise and unambiguous, but require uniform distribution of tracer in the calcium source, a feature not possible for pre-formed or commercial sources. The pharmacokinetic methods are the gold standard for drugs, but tend to be insensitive for substances normally present in large quantities in the body anyway (such as calcium), and they also require larger than typical dose sizes in order to ensure a measurable effect. They measure mainly the rise in serum calcium that inevitably accompanies absorption of calcium from the gut into the bloodstream.

The pharmacodynamic methods measure 1) the rise in urine calcium or the fall in parathyroid hormone (PTH) that are the consequence of the absorptive rise in serum calcium, or 2) the change in bone mass, density, or remodeling rates produced by the absorbed calcium. The pharmacodynamic methods are the least sensitive, since what they measure is influenced by many factors in addition to absorption.

15. Absorbed calcium does not so much "go to bone" as it prevents the body from continually accessing the bony calcium reserves. Calcium is lost every day through skin, digestive secretions, and urine. The purpose of daily calcium intake is to offset these losses. If absorbed calcium is not sufficient for that purpose, the body's control systems tear down microscopic volumes of bone to scavenge their calcium. However, during growth or when patients are being treated with bonebuilding drugs such as teriparatide, the calcium of diets or supplements does "go to

bone." Nevertheless, supplement use in most contexts serves mainly to *protect* existing bone, not to *build* bone.

16. Bone is continually undergoing remodeling, a process closely analogous to the structural remodeling of buildings. First, old or damaged bone is removed ("resorption"); then new bone is laid down in its place ("formation"). At a particular site, this process takes several months in older adults. The most basic purposes of remodeling are to replace damaged bone and to reshape bone so as better to fit it to resist current load patterns. Additionally, remodeling serves to release calcium into the blood stream. For this reason, remodeling will typically be high (higher than needed for structural repair) in individuals with low calcium intakes.

17. Volumes of bone undergoing remodeling, contain little or no mineral (i.e., the calcium salt that makes bone hard), and hence this bone is not detected by the usual clinical methods (DXA) for assessing bone mass or density (BMD). If bone remodeling activity increases (for whatever reason), *measurable* bone mass declines, and if remodeling decreases, measurable bone mass increases. But *actual* bone quantity changes little if at all with such changes in remodeling activity (although the bone becomes locally more dense).

18. Because of the asynchrony of remodeling (resorption first, followed by formation later), a decrease in remodeling activity (such as might be produced by calcium, vitamin D, or several of the bone-active pharmacologic agents) results in an

apparent increase in bone mass. This is simply because activation of new remodeling loci is reduced, while previously activated units are coming back into service at the rate at which they were removed several weeks or months earlier. This increase continues for weeks or months (essentially for the length of the remodeling cycle), then levels off, either to the prior steady state or to a new steady state produced by the intervention. Thus these changes are referred to as "remodeling transients." They do not so much reflect *gain* of bone as reclaiming of what had been out of commission for remodeling. However, this is not to suggest that this change is not without benefit in many cases. If the bone removed for its calcium had been structurally sound, then removing it weakens the bone locally, and lessening of that process helps protect the skeleton.

III. SCOPE OF WORK AND CONCLUSIONS

19. The FTC staff has asked me to read certain materials (LL650 through LL1068 (Index attached as Exhibit 2)) and evaluate, from my perspective as an expert, whether these materials substantiated certain claims, set forth below. I have read the materials provided. In broad generalities they consist of copies of full text articles published in scientific journals, copies of abstracts of articles, miscellaneous correspondence, three patents, a marketing consultant's report, and recorded interviews with Takuo Fujita, the developer of the Japanese product which is

marketed in the United States as AdvaCAL. Much of the material supplied is duplicative (some several times over). Some of it I had seen previously.¹

Approximately 30–40% of the submitted evidence represents, or is based upon, articles by recognized scientists from around the world establishing the value of increasing calcium intake. In my view this evidence is not pertinent, inasmuch as it is not in dispute and, in fact, it serves as a basis for official U.S. government policy statements. That policy, stated in many formats, is that increasing calcium intake above levels prevailing in the U.S. population will confer bone benefits.

In several instances, individual reports taken from this body of generally accepted evidence are used to provide a basis for quantifying and comparing the effects of various calcium sources on bone mineral density and fracture rate, for example, as used in LL793 (Exhibit 4). In general, the results used for particular products are not representative of the totality of the evidence relating to the specific product or outcome, and in no instance were those studies performed in a way that would allow side-by-side comparison of the products concerned with respect to outcomes of interest.

An instance will serve to exemplify this problem (which occurs in this respect many times over). In LL793 (Exhibit 4), the calcium supplement, calcium-citrate-

¹ In 1999 Lane Laboratories had asked me to review certain of these materials and to comment on their validity and significance. A copy of my opinion is attached as Exhibit 3.

malate (CCM), is represented as producing bone loss, whereas in the same graph, calcium carbonate and AdvaCAL are represented as producing bone gain. CCM is generally recognized to be the best absorbed calcium supplement in widespread market use, certainly at least as good as, if not better than, for example, calcium citrate or calcium carbonate. Since, as enshrined in official U.S. policy statements, the effect of calcium on bone mineral density is due entirely to the quantity absorbed, the paradoxical relationship depicted in LL793 (Exhibit 4) is not plausible. Furthermore, if one examines the paper behind the CCM figure, one notes that there was a placebo group that lost 3.5% of bone mass over two years, whereas the CCM group lost 1.25%, or about only one-third as much. That represents a substantial benefit for women who would otherwise be losing a great deal more bone. By contrast, other studies of CCM in women with stable bone mass show an apparent gain in bone due to a positive bone remodeling transient (see II. Background <u>Considerations 17–19</u>). In brief, the results one gets from a given intervention depend heavily upon the underlying biology of the group concerned, and comparisons between products can be made only within such groups, not across groups that otherwise differ in important respects. In general, the same types of criticisms can be made about the fracture comparisons in the advertising copy in LL793 (Exhibit 4), but here there are additional problems, as well (see below).

There is a second instance, which typifies the generally poor investigational design of many of the studies involving AdvaCAL, as well as the tendency to misinterpret the results. I refer to two papers by Fujita and colleagues (LL667-671 and LL750-756). The first was published in the journal, *Calcified Tissue* International in 1996 (Exhibit 5) and describes results of a study that had, seemingly, been previously published in a Japanese journal (LL664-666), and had described results in individuals treated with three products, one called AAACa (presumably identical to AdvaCAL),² calcium carbonate, and placebo, in elderly, hospitalized women with a mean age of 80. The effects on bone mineral density of the three treatments, as set forth, for example, in Table 1A (LL668 - Exhibit 5) seemed to indicate improvement in bone mineral density in all three groups so that, by 24 months, BMD had risen by 0.049 g/cm² (7.8%) in the AAACa group, by 0.009 (1.5%) in the calcium carbonate group, and by 0.010 (1.6%) in the placebo group. But placebo-treated, 80-year-old women do not gain bone over a 24-month period, as this dataset taken at face value would suggest.

The most likely explanation for this seemingly anomalous fact is found in the numbers of patients available for measurement at each time point. The three groups, initially, contained 19, 17, and 20 individuals, respectively. By the 24-month time

² Because formulation can have a major effect on absorbability (See <u>II.</u> <u>Background Considerations 14</u>), identity of the marketed and tested products is critically important.

point, these numbers had fallen to 5, 6, and 7. Two points need to be made: the sickest, frailest individuals – the ones with the lowest starting BMD values – are almost certainly the ones who were lost from study; thus every time a sick individual with low BMD dropped from study, the average for the group remaining in the study rose, of mathematical necessity. Note that two-thirds to three-fourths of all the subjects entering the trial had dropped by the 30 month point. Even had that not been the case, it is not scientifically valid to compare *group* mean values with this type of study design. It is the *within-individual change* which is the appropriate variable to be evaluated, and that information is not supplied in this paper. Furthermore, even had it been supplied, the remaining sample size would have been too small to permit any kind of useful conclusion.

This same paper contains a number of internal inconsistencies, not explainable except possibly by the bias that is conferred by comparing means at different time points when the numbers of subjects in each measurement group differ (see above). Table 3A on LL669 (Exhibit 5) is a case in point. It contains values for urinary Ca:Cr ratios in the three treatment groups. The Ca:Cr ratio is effectively equivalent to urinary calcium excretion (with the creatinine serving to correct for incomplete collections and like errors). Urinary calcium excretion is a widely used measure to evaluate calcium absorption. It is a relatively weak and insensitive measure, and is not one that I would recommend; nevertheless, its use is based on the fact that when

one absorbs calcium, some of the absorbed calcium spills into the urine, thereby raising urine calcium. Calcium absorption is never associated with a fall in urine calcium. As Table 3A shows, however, using only the group means at the various time points, the urinary Ca:Cr ratio falls from a pre-treatment value of 0.344 to a 30-month value of 0.173 in the individuals treated with AAACa. Thus the urine calcium, as reported, shows no evidence whatsoever of any calcium absorption, and without calcium absorption there cannot have been an effect on bone mineral density. But once again, the appropriate measure would have been the within-individual change, and that is not supplied by this paper. This inconsistency highlights why analysis of group means in a repeated measures design is invalid. In this case it produces blatantly implausible results. (Incidentally, all three treatment groups showed comparable "declines" in the Ca:Cr ratio.)

No mention of fracture is made in this paper, but fractures observed in apparently the same trial are reported in LL750-756, a paper published in the *Journal* of Bone and Mineral Metabolism, 2004 (Exhibit 6), which is described as a "reappraisal" of the data from the study first published definitively in *Calcified Tissue International* (Exhibit 5). As with the earlier paper, we still have no data on within-subject changes, and the fracture figures cited are impossible to interpret since they are expressed as numbers of fractures per 1,000 subject years, without providing the number of subject years actually experienced; moreover the absolute number of

fractures is, itself, not even mentioned. Since the study duration was 2.5 years, and by the end of the study, three-fourths of the subjects had dropped out, it can be roughly estimated that there were perhaps no more than 10 actual person years of observation in each group. While the paper reports that no fractures occurred in the AAACa-treated group, a finding of zero out of 10 is actually consistent with a true fracture rate of anywhere from 0% to as high as 31%. The confidence intervals for the estimated fracture rates for the three groups are not given, and should have been. In any event, Dr. Fujita himself, in his interview (LL766-773) (Exhibit 7) acknowledges that the number of subjects in this study was too small to support a claim of zero fractures.

Lane Labs also cites as support for its claims a paper published in the *Journal* of *Bone and Mineral Metabolism* in 1997 (LL672-675). There is no side-by-side comparison here with other calcium salts; hence this study cannot be used to support a claim of superiority for AAACa. This study was apparently the source of the value used in the left-hand bar graph in LL793 (Exhibit 4). In its original context, the 2.6% improvement at 24 months is about what might be expected for any good calcium supplement. As the data in Table 2 (LL673) show, most of this change was achieved by 6 months, with very little further improvement thereafter. This is the type of behavior typically seen with the remodeling transient (see above), such as might be produced by calcium.

Finally, Lane Labs cites as support for its claims of superiority a paper published in the *Journal of Bone and Mineral Metabolism* in 2000 (LL676-679). This study found no significant change at the lumbar spine for any product (and no difference between products). There was a statistically significant increase in radial BMD for AAACa, but not for the other preparations, but there was no statistically significant difference between AAACa and Calcium Carbonate. Moreover, the groups were not well matched, both on age and on baseline BMD, and the sample sizes were extremely small (between 6-11 individuals per group). This study thus produced an indeterminate result. Such studies should not be done, as they are clearly underpowered, and if done, should not be published.

20. The FTC staff has asked me to evaluate the following three groups of claims:

21a. AdvaCAL is more absorbable than other calciums

Relatively few of the materials provided contain information with respect to relative absorbability of calcium from AdvaCAL. One such would be LL685-689, a report vaguely describing a study in parathyroidectomized rats given massive calcium loads by gastric gavage. This paper seems to be an evaluation of the value of added HAI to a product called AACa, rather than of AdvaCAL absorbability, *per se*. While HAI was associated with apparently higher levels of calcium absorption, there was no dose response relationship across a broad range of HAI doses (10,000-fold). The

findings are thus very difficult to interpret. The same paper, by contrast, showed that in a different animal model (rats fed a low calcium diet), AACa alone was as effective as AACa plus HAI. Another paper (LL690-695) by Fukuta contains information on calcium absorbability, but the methods are not mentioned and Fig. 1 in that paper shows implausibly high elevations of serum calcium after intraintestinal injection. This portion of the Fukuta paper may have been a reference to the study cited under LL685-689, but this is not clear. There are no human studies in the body of evidence describing calcium absorbability from AdvaCAL, alone or in comparison with other calcium sources.

Nor is there evidence in the material provided me to support a claim that, in humans, AdvaCAL is 3 times more absorbable than other calciums. It is useful to bear in mind that the calcium absorption fraction for most calcium sources (including milk) at a 300 mg load is approximately 0.30, and for a source to be 3 times as absorbable as that, the fractional absorption would have to be 0.90 (or 90% of the ingested calcium absorbed). Except in low birth weight newborns with an immature gut, no calcium absorption fractions remotely close to 0.90 have ever been reported.

I have also, independent of this action, investigated the absorbability of calcium from AdvaCAL under a contract with Lane Laboratories (Exhibit 8). This work was performed in 2000 and reported to Lane Laboratories in December of that year. Briefly, absorbability of calcium from AdvaCAL was compared to the absorbability

of calcium from CitracalTM (Mission Pharmacal) using pharmacokinetic methods in a randomized cross-over design in 24 healthy postmenopausal women. Calcium load for the two sources was effectively identical (955–995 mg). With the pharmacokinetic methods, comparison is made between the degree of elevation of the serum calcium concentration consequent upon absorption of calcium from the gut into the blood stream. This elevation is measured as "area under the curve (AUC)". In my study, AUC for AdvaCAL was 3.148 mg·hr/dL, and for Citracal[™], 4.386 mg⋅hr/dL. (The higher value for Citracal[™] indicates about 30% greater absorption of its calcium.) Converting these AUC values into absorption fractions revealed that fractional absorption for AdvaCAL was 0.218, and for Citracal, 0.284. The conclusion that can be reached from these data is that the absorption of calcium from AdvaCAL is good, but not as good as the absorption from Citracal, and certainly not superior.

21b. <u>AdvaCAL is the only calcium product that can "build bone</u>." <u>AdvaCAL</u> <u>can increase bone mass density a specific amount</u>. (For example, increases bone density in women by as much as 10% a year; 13.5% increase in bone density after 24 months; 3.8% increase in bone density after 4 months; 3.2% increase in bone density for elderly women in 2 years; 2.5% increase in bone density for post-menopausal women in 2 years; those suffering from osteoporosis (ages 51-83) increased BMD by 4.5% over 3 years. <u>AdvaCAL builds more bone than other calcium products</u>. (For

example: Clinical studies show AdvaCAL is substantially superior to Ca Carbonate, Ca Citrate Malate and Ca Hydroxy Apatite in increasing spinal bone density in postmenopausal women and elderly women; increases bone density in post-menopausal women (approximately 2.6% over 2 years) compared with Calcium Citrate (approximately 1% over 2 years) and Calcium Citrate Malate (approximately -1.2% over 2 years); increases bone density in elderly women (approximately 3.1% over two years) compared with Calcium Carbonate (approximately 0.8% over 2 years) and Calcium Hydroxy Apatite (approximately 1.9% over 2 years). <u>AdvaCAL is</u> <u>Comparable or Superior to Rx Drugs in Building Bone</u>.

These claims have two components: "building" bone and superiority relative to other products. No calcium source, by itself – and that includes AdvaCAL – literally builds *new* bone. While calcium is one of the basic components of bone, it is not a sufficient stimulus by itself to cause more bone to be formed. Individuals who are given bone active agents, particularly of the anabolic sort (e.g., Eli Lilly's ForteoTM) do, in fact, build bone. And they need a high calcium intake in order to support that bone building. In such circumstances calcium helps build bone, but it does not do so by itself.

However, there is one sense in which the changes produced by supplemental calcium might be interpreted as building bone. Because of the reduction of remodeling which is produced by calcium supplements, there is an increase in

measurable bone mineral density, as noted above, and this could be interpreted as consistent with the concept of "building bone." But as noted in <u>II. Background</u> <u>Considerations 17–19</u>, the increase in measurable bone mineral represents bone that was actually already there, but not fully mineralized, and therefore not measurable. This is not to minimize the value of reclaiming bone that had been out of commission, for it is likely that such reclamation is in large part responsible for the reduction in fracture risk. But it is to stress the distinction between *building* new bone, and *reclaiming* bone undergoing remodeling.

With respect to the matter of superiority, there is nothing, in my judgment, in the evidence provided me, which would indicate that AdvaCAL calcium has effects that are more striking in this regard than any other calcium supplement. To the extent that one accepts the effects of calcium on "filling in the remodeling space" as being equivalent to "building" bone, then AdvaCAL shares in those effects, as do other properly formulated calcium supplement sources.

Additionally, nothing in the materials supplied me (LL650 through LL1068 -Exhibit 2) provides credible scientific support for the specifics of the aforementioned claims. It is possible to envision particular situations (see below) in which increases of the magnitude stated in the claims quoted above might be plausible. In general, however, they would be quite unusual. Whether *any* calcium source will increase bone mass density by a specific amount depends mainly on certain features of the study participants and on study details. Also, the word "increase" needs to be more precisely defined. For example, if a group of individuals, on average, is losing bone because of inadequate calcium intake, then the use of calcium supplements will slow or stop that loss. While not technically an "increase" as would be intended in common English usage, this is nevertheless an improvement. Also, in a parallel, two-group study, the supplemented group will end up with more bone than the unsupplemented. So if the data were plotted as a bar graph, the supplemented group's BMD value would be *above* the unsupplemented, and might thus seem to indicate an increase. However, a higher value relative to a contrasting treatment, while useful, is not the same thing as a true "increase" from baseline.

Further, and as set forth in <u>II. Background Considerations 17–19</u>, calcium supplements, in common with several other bone active agents, reduce bone remodeling and produce a transient increase in measurable bone mineral. If the individuals in which a particular supplement is being tested have a high rate of remodeling, then the size of the remodeling transient will be correspondingly large, and if the basic rate of bone loss is close to zero, then this large transient will produce a measurable *increase* in bone mineral. This is termed "filling in the remodeling space" and does not represent so much *new* bone, as bringing bone that had been

under repair back into service. Nevertheless, this change *is* measured as an increase in bone mineral density and it is likely to result in bone strengthening.

At the same time I must also stress that, because a fraction of the AdvaCAL calcium is absorbed, it would be predicted to produce the benefits that accrue to calcium generally, and these would include the slowing or cessation of age-related bone loss, coupled with a positive bone remodeling transient.

Finally, there is no evidence in the materials supplied me to support a claim of comparability (or superiority) relative to pharmacologic agents, and I am not aware of any other evidence that would substantiate it. Most of the pharmacologic agents have been tested against a "placebo" group that actually consisted of a calcium supplement, usually in a dose on the order of 500 mg/d. The reported fracture reduction values for these agents were, therefore, relative to what one would get with a modest supplemental calcium intake. In order to be approved by the FDA, they had to have exhibited statistically significantly greater effects (change in BMD and reduction in fracture) than the calcium-treated, control group. By contrast, the trials of calcium with fracture outcomes just cited used a low calcium, true placebo control. Thus the potency of calcium relative to the pharmacologic agents is unclear, as the two classes of agent have not been tested side-by-side in a properly designed trial. Nevertheless, there is a scientific consensus that calcium, while useful and necessary, is not as potent in reducing fracture risk as the bone active pharmacologic agents

taken with calcium. In my judgment, it would be potentially dangerous to tell patients at high risk for fracture that they needed only a particular supplemental form of calcium, as doing so might cause them to forego needed pharmacotherapy.

21c. <u>AdvaCAL users have fewer fractures than users of other calcium</u> <u>products. AdvaCAL users can avoid fractures.</u> (For example, 100% fracture reduction for elderly patients over 3 years; "You don't have to be in a nursing home because you broke your hip – all you have to do is take your AdvaCAL to prevent that.")

These two claims would seem to contradict one another, inasmuch as "fewer fractures" implies that AdvaCAL users would have *some* fractures, whereas the second claim suggests *no* fractures. In any event, AdvaCAL users could be expected to have fewer fractures than non-users of calcium supplements, but the evidence provided (LL650-LL1068 - Exhibit 2) does not provide evidence to substantiate a claim of superior fracture reduction. With the exception of LL667-671 (Exhibit 5), there are no randomized, side-by-side comparisons of AdvaCAL with other calcium supplements, and the evidence cited in advertisements such as LL793 (Exhibit 3) come from very different studies involving very different populations and treatment conditions. Furthermore, the figures cited for such products are not representative of the totality of the evidence with respect to the individual sources used in this comparison.

With respect to the claim of avoiding fractures, I know of no evidence, including that provided by Lane Laboratories, to substantiate a claim that patients ingesting AdvaCAL or any calcium supplement could "avoid" fractures. Indeed, as already noted, Dr. Takuo Fujita, in a recorded interview in one of the items of evidence (LL766–LL773 - Exhibit 7), himself noted, in commenting on his paper in which fractures were recorded, that the sample size was not large enough to substantiate a claim of "no fractures." I would expect that users of any absorbable calcium supplement, including AdvaCAL, will have a reduced fracture risk, but not zero. No bone active agent, nutritional or pharmaceutical, can prevent all fractures (the usual meaning of "avoid"). Adequate calcium intake, particularly when coupled with normal vitamin D status, has been reported in well-controlled studies to reduce fractures in various studies and at various skeletal sites by from 30 to 55%. Similarly, various pharmacologic agents have been shown to reduce fracture risk by roughly 40 to 70%. Nothing reduces fractures by 100%. Incidentally, and as noted above, it would be dangerous, in my judgment, to tell consumers at high risk for fracture that a calcium source alone provided as good fracture protection as approved pharmacologic agents.

22. Because cost is an important consideration for consumers, the FTC staff has asked me to include a paper describing a study my colleagues and I performed comparing absorbability of calcium from two marketed calcium salts, and evaluating

their relative cost-effectiveness. (Exhibit 9) In brief, calcium citrate and calcium carbonate exhibited identical absorbability, but because calcium citrate was the more expensive of the two, calcium carbonate delivered a greater amount of calcium into the body for the same dollar cost.

IV. GENERAL REQUIREMENTS FOR RELIABLE SCIENTIFIC SUPPORT FOR DEFENDANT'S CLAIMS

23. The claim of superiority of one product relative to another requires a double-blind, randomized trial, utilizing either parallel side-by-side treatments, or a within-subject cross-over. The latter is better suited to evaluation of absorbability since it can be done in a short period of time and has lower sample size requirements, whereas the former is necessary for detection of differences in BMD or fracture rate, since these outcomes require years for their effect to become apparent. With either design, quantitative comparisons between products or treatments can be made only for products or treatments randomly allocated to participants *in the same study*. Moreover, when the conclusions from such a study involve *changes* in some measurable variable (such as fracture rate, BMD, or absorbability), it must be the changes produced under the two treatment conditions that are evaluated and tested statistically.

Having said that, there are two features of AdvaCAL which require some nuancing of the foregoing.

First, AdvaCAL is a calcium source, and, as noted in <u>II. Background</u> <u>Considerations, 10–13</u>, once calcium from a particular source is absorbed, it shares in all the benefits of calcium generally. Briefly, to claim greater bone benefits, one needs only to show greater absorbability, because, for the same ingested load, the better absorbed product delivers more calcium into the blood stream. (At the same time it is necessary to point out that virtually all calcium sources can potentially deliver the same quantity of calcium into the blood stream by the simple device of adjusting the size of the dose.)

The second issue relates to the HAI ingredient in AdvaCAL, with respect to which most of the evidence supplied me is relatively silent. If HAI were to have some bone activity in its own right, then that possibility would have to be tested in the same way that the pharmacologic agents are tested, i.e., with a large, placebocontrolled trial. On the other hand, if the activity of HAI (to the extent that such exists) is confined to promoting calcium absorption (as is implied in some of the evidence provided), then simple tests of the absorbability of AdvaCAL should suffice to evaluate such claims.

V. CONCLUSION

24. I understand that the FTC uses a standard of "competent and reliable scientific evidence" in evaluating claims. It is my considered judgment, as an expert in this field, that no competent and reliable scientific evidence exists to support the claims cited above for Lane Laboratory's AdvaCAL. Thus, my conclusion is that the evidence provided does not satisfy the general requirements for the establishment of a claim of superiority for any product, relative to any other. While AdvaCAL can be a useful nutritional supplement, in terms of absorbability, effect on bone mineral density, and effect on fracture rate, AdvaCAL is not superior to other calcium sources.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed at Omaha, Nebraska on Jennary 3, 2006.

Robert P. Heaney, M.D.

Exhibit 1

CURRICULUM VITAE ROBERT P. HEANEY, M.D.

Current Position:

John A. Creighton University Professor Creighton University Omaha, NE 68178 (402) 280-4029 – Phone (402) 280-4751 – FAX rheaney@creighton.edu – e-mail

Personal:

Born – November 10, 1927, Omaha, Nebraska Religion – Roman Catholic Marital Status – Married (Barbara Reardon Heaney, M.D.) Children – Seven Home Address – 5210 Burt Street, Omaha, NE 68132

Education:

B.S., Magna cum laude (Chemistry Major), 1947 Creighton University, Omaha, Nebraska

M.D., Creighton University School of Medicine, 1951 Omaha, Nebraska

Internship – St. Louis City Hospital, 1951-1952 St. Louis, Missouri

Residency – St. Louis City Hospital Service of St. Louis University (Internal Medicine) 1952-1953

Additional Graduate Training:

Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma American Cancer Society Clinical Fellow, 1953-1954 Public Health Service Post-Doctoral Fellowship (NCI) 1954-1955 National Institute of Arthritis & Metabolic Diseases Bethesda, Maryland, Clinical Associate 1955-1957

Uniformed Service:

U.S. Public Health Service (Sr. Ass't. Surgeon) 1955-1957

Teaching & Administrative Appointments:

University of Oklahoma School of Medicine Instructor, Department of Medicine, 1954 George Washington University Clinical Instructor, Department of Medicine, 1955 Creighton University Assistant Professor, Department of Medicine, 1957 Associate Professor of Medicine, 1960 Acting Chairman, Department of Medicine, 1960 Professor of Medicine, 1961 Chairman, Department of Medicine, 1961-1969 Head, Section of Endocrinology & Metabolism, 1969-1971 Vice President for Health Sciences, 1971-1984 John A. Creighton University Professorship, 1984-Creighton University Chair, Presidential Task Force for Dominican Republic Programs, 1995-97

Chair, Presidential Task Force on Compliance Issues, 2000

Chair, Presidential Task Force on Clinical Research, 2003

Membership in Professional Societies:

American College of Physicians (Fellow) American Institute of Nutrition (Fellow) now American Society for Nutritional Sciences American College of Nutrition (Fellow) American Society for Bone and Mineral Research American Society for Clinical Nutrition International Conferences on Calcium Regulating Hormones, Inc. Physicians for Social Responsibility The Endocrine Society

Scientific Committee Memberships & Consultantships:

National Institute of Dental Research, Dental Training Committee, Member, 1962-1966 National Aeronautics and Space Administration, Manned Spacecraft Center, Consultant, 1964-1965 National Institutes of Health, General Medicine (B) Study Section; Member, 1966-1970; Chairman, 1970-1971 Central Society for Clinical Research, Counselor, 1966-1969 U.S. Veterans Administration, Endocrinology and Metabolism Review Panel, Member, 1969-1972 National Academy of Sciences, National Research Council, Calcium Metabolism Review Panel, Member, 1970-1971 National Institute of Arthritis and Metabolic Diseases, Orthopaedic Training Committee, Member, 1971-1973 National Institute of Dental Research, ad hoc Committee for Review of Mineralization Research Effort, Chairman, 1973 National Aeronautics and Space Administration, American Institute of Biological Sciences Medical Sciences Advisory Panel, Member, 1976-1980 National Institute for Arthritis Metabolic and Digestive Diseases; Arthritis, Bone and Skin Program Project Review Group; Member, 1977-1978

National Institute of Dental Research Special Grants Review Committee, Chairman, 1982-1986

The National Osteoporosis Foundation, Scientific Advisory Committee, 1986-1991; Board of Directors, 1990-2002; Emeritus Board, 2002; Co-Chair Education Committee, 2002-2005; Chair, Network Task Force, 2001-2002; Scientific Advisory Council, 2005-2008.

Nutrition Research Science Advisory Committee of the National Dairy Council, 1986-1989; Chairman, 1987-1989

Scientific Visiting Committee of USDA Human Nutrition Research Center on Aging at Tufts University, 1986-

Office of Technology Assessment, US Congress, Scientific Advisory Panel on Osteoporosis, Chairman, 1990-1994

Calcium Information Center, Scientific Advisory Board, 1991-

National Osteoporosis Data Group (NODG), 1993-

NIH. Postmenopausal Estrogen/Progestin Intervention (PEPI),

Data and Safety Monitoring Board, 1991-1994

NIH, Womens' Health Initiative, Data and Safety Monitoring Board, 1993-2004

Nutrition Advisory Group/Coca-Cola Company, 1994-1995

NASA Life Sciences Advisory Sucommittee, 1994-1997

National Nutrition Advisory Council/Administration on Aging, DHHS, 1995–1997 MilkPEP Medical Advisory Board, 1994-

Panel on Calcium and Related Nutrients, Food & Nutrition Board, NAS, 1995-1997 GlaxoSmithKline Calcium Advisory Board, 1997-2005

National Bone Health Campaign Scientific Task Force, 1999-

NAMS Consensus Opinion on the Role of Calcium in Peri- and Postmenopause, Editorial Board Chair, 2000; 2006

Duke Clinical Research Institute, Data and Safety Monitoring Board Chair, 2002–2003 Surgeon General's Report on Osteoporosis and Bone Health, Writing Committee, 2003 ConAgra Scientific Advisory Board, 2006–2008

Educational Committee Memberships & Consultantships:

Association for Academic Health Centers, Board of Directors, Member, 1975-1978; Program Chairman, 1977; Chairman-Elect, 1978-1979; Chairman, 1979-1980

ADA Council on Dental Education, Special Review Committee on "Dental Education in the United States 1976" Member, 1978-1979

Chairman, ad hoc Consultant Panel for Peter J. Liacouras, President, Temple University, in regard to Temple University School of Pharmacy, 1985
Pew National Dental Education Program Advisory Committee, 1984-1992
National Commission on Nursing Implementation Project, 1985-1987
Committee of Visitors, Vanderbilt University School of Nursing, 1987-

Civic and Church Committee Memberships & Consultantships:

- Health Planning Council of the Midlands, Member, Board of Directors, 1971-1981; Member, Executive Committee, 1972-1979; Vice President, 1974-1978; Secretary, 1979
- Archdiocese of Omaha: Archdiocesan Commission on Sacred Liturgy, Music, and Art; Member, 1968-1981
- St. John's Parish, Omaha, Parish Council, Member 1978-1986; Chairman, 1980-1981; Member 1994-
- Loyola University, Chicago, Illinois, Board of Trustees, Member, 1981-1990; Medical Center Committee 1981-1992

Omaha Safety Council, Member, Board of Directors, 1986-1989 Wellness Councils of America Medical Advisory Board, 1997-

Editorial Boards:

Calcified Tissue (Research) International, 1966-1977, 1978-1986, 1994-1999 Journal of Clinical Endocrinology and Metabolism, 1967-1969; 2002-2006 Journal of Laboratory and Clinical Medicine, 1976-1982 BONE, (previously Metabolic Bone Disease and Related Research), 1981-1994 BONE, (merger between BONE and Bone and Mineral), 1994-Bone and Mineral, 1985-1994 Dairy Bureau of Canada's Nutrition Quarterly, 1986-Osteoporosis International, 1990-

European Journal of Experimental Musculoskeletal Research, 1990-

American Journal of Clinical Nutrition, 2006-2008

Honors and Awards:

Alpha Sigma Nu

Alpha Omega Alpha

Lederle Medical Faculty Award 1960-1963

Chairman, Gordon Research Conference, (Bones and Teeth) 1966

Kappa Delta Award (American Academy of Orthopaedic Surgeons), 1970

Creighton Distinguished Faculty Award, 1974

Network for Cont. Med. Educ. Ohio State Award for the program: "Osteoporosis:

A Disorder of Bone Remodeling," 1979

Combined Health Agencies Drive of Omaha, Health Citizen of the Year Award, 1984 Creighton University, Alumni Achievement Citation, 1988

The American Dietetic Association, Honorary Membership, 1990

Third International Symposium on Osteoporosis, Copenhagen, Honorary President, 1990 Creighton University, Distinguished Research Career Award, 1991

Fellow, American Institute of Nutrition, 1993

Frederic C. Bartter Award, 1994, American Society for Bone & Mineral Research 2000-2001 Best Scientific Paper Award, American College of Nutrition

State of Nebraska, Admiral in the Great Navy of the State of Nebraska, 2003 Institut Candia Scientific Prize for 2003

E.V. McCollum Award, 2003, American Society for Clinical Nutrition Laureate Award, 2003, Nebraska Chapter of the American College of Physicians 2004 North American Menopause Society Innovations in Osteoporosis Award

Named Lectureships:

- The Second Annual Drummond Lecture in Medical Ethics, St. Louis University Medical Center, 1987
- The Seventh Annual Dorothy E. Vossen Lecture Series in Nursing, Creighton University, 1987
- The Dean's Distinguished Lecture Series, School of Nursing, University of Pennsylvania, 1987
- James F. Sullivan Lectureship, Department of Internal Medicine, Creighton University, 1992

American Dairy Science Association, First ADSA Foundation Lecture, 1993 Boyd O'Dell Lectureship, University of Missouri – Columbia, 1995 Ethel Austin Martin Distinguished Lectureship, SD State University, Brookings, 2000 Lila Wallis Distinguished Visiting Professor on Women's Health, Cornell University Medical Center, New York, 2003

19th Annual Boy Frame Memorial Lecture, Henry Ford Hospital, Detroit, 2005 Campbell Lecture in Nutrition Education, University of Guelph, Guelph, Ontario, 2006

PUBLICATIONS ABSTRACTS

A-1. Eliel LP, Heaney RP. The effect of variations in amino acids intake and protein deficit on the metabolic response of soft tissue and bone to cortisone acetate. J Clin Invest 33:930, 1954.

A-2. Heaney RP, Eliel LP, Joel W, Stout H. Hyperphagia, obesity and duodenal ulcer associated with hyperthalamic leukemic infiltration. J Clin Endocrinol Metab 14:829-830, 1954.

A-3. Heaney RP, Eliel LP. Changes in intracellular composition of human leukemic tissues in response to anti-leukemic therapy. Proc Am Assoc for Cancer Res 2:23, 1955.

A-4. Eliel LP, Heaney RP. The effects of protein deprivation on the response of lymphoid tumors and normal tissues to steroid hormones. Proc Am Assoc for Cancer Res 2:14, 1955.

A-5. Heaney RP, Eliel LP. Changes in leukemic tissue composition and metabolic balances produced by a purine antagonist (6-mercaptopurine) in man. Clin Res Proc 3:79, 1955.

A-6. Eliel LP, Heaney RP. The effects of steroid hormones on anabolism and catabolism of normal tissues and lymphoid tumors in humans on protein-free diets. J Clin Invest 6:932, 1955.

A-7. Heaney RP, Whedon GD. Calcium-45 dynamics in human metabolic bone disease. Program, Endocrine Society, 39th Annual Meeting, New York, 1957.

A-8. Heaney RP. Radiocalcium metabolism in human disuse osteoporosis. J Lab Clin Med 56:825, 1960.

A-9. Heaney RP. Rate of calcium equilibrium in human tissues. J Lab Clin Med 60:882, 1962.

A-10. Skillman TG, Heaney RP. Endogenous intestinal calcium secretion. J Lab Clin Med 60:1018-1019, 1962.

A-11. Heaney RP, Skillman TG. Normal calcium kinetics: Application of a newly derived composite reference standard. J Lab Clin Med 62:882, 1963.

A-12. Heaney RP, Kramar P. Mechanism of development of osteoporosis in the immobilized rabbit calcaneus (trueta preparation). Proc of Orthop Res Society, January, 1965.

A-13. Sullivan JF, Heaney RP. Zinc 65 metabolism in patients with cirrhosis. J Lab Clin Med 38:76, 1965.

A-14. Heaney RP. Kinetic studies in human osteoporosis. J Bone Jt Surg

A-15. Heaney RP, Skillman TG. Calcium metabolism in normal human pregnancy. J Clin Invest 49:41a, 1970.

A-16. Heaney RP, Saville PD. Dietary calcium, calcium absorption, and skeletal interrelations. Proc 8th European Symposium on Calcified Tissues, Israel, March-April, 1971.

A-17. Heaney RP, Saville PD. Radiogrammetric indices in normal women: Their relation to body size and calcium metabolism. IRCS International Research Communications System, April, 1973.

A-18. Heaney RP, Recker RR, Saville PD. Calcium balance and calcium requirements in middleaged women. Clin Res 22:649A, 1974. A-19. Heaney RP, Recker RR. Estrogen effects on bone remodeling at menopause. Clin Res 23:535A, 1975.

A-20. Recker RR, Saville PD, Heaney RP. Sex hormones or calcium supplements diminish postmenopausal bone loss. Clin Res 24:583A, 1976.

A-21. Recker RR, Heaney RP. Milk supplements and bone and calcium metabolism in healthy postmenopausal women. Clin Res 32:406A, April 1984.

A-22. Recker RR, Gallagher JC, Heaney RP. The metabolic effects of treatment with calcitriol in patients with postmenopausal osteoporosis. Clin Res 32:406A, April 1984.

A-23. Heaney RP, Recker RR. The anion effect during calcium supplementation. Clin Res 32:520A, April 1984.

A-24. Heaney RP, Recker RR. Distribution of calcium absorption in middle-aged women. Clin Res 33:889A, October 1985.

A-25. Weaver CM, Heaney RP, Martin BR. Oxalic acid inhibits calcium absorption. Proc Soc Exp Biol Med 46(3):631, 1987.

A-26. Heaney RP. Qualitative factors in osteoporotic fracture: The state of the question. International Symposium on Osteoporosis Abstracts, p. 24, 1987.

A-27. Heaney RP, Avioli LV, Chesnut CH, Recker RR, Gallagher JC. Is bone loss the cause of osteoporotic fracture or its consequence? J Bone Miner Res 3:S88, 1988.

A-28. Avioli LV, Brandenburger G, Chesnut CH, Gallagher JC, Heaney RP, Lappe J, Recker RR. Ultrasound transmission velocity in screening for bone fragility. J Bone Miner Res 3:S215, 1988.

A-29. Davies KM, Recker RR, Heaney RP. A vertebral radiogrammetric standard. J Bone Miner Res 3:S124, 1988.

A-30. Recker RR, Kimmel DB, Davies KM, Barger-Lux MJ, Heaney RP. Determinants of spinal mineral content in normal women. J Bone Miner Res 3:S86, 1988.

A-31. Barger-Lux MJ, Heaney RP, Recker RR. Time course of calcium absorption in humans: evidence for a colonic component. J Bone Miner Res 3:S159, 1988.

A-32. Stegman MR, Barger-Lux MJ, Heaney RP. Caffeine effects on calcium physiology in a crossover study: issues in methods and analysis. Poster Session, Tenth Annual Meeting, Society for Clinical Trials, May, 1989, Minneapolis, Minnesota.

A-33. Stegman MR, Heaney RP, Recker RR, Davies KM, Kelsey WP. Fluoride exposure and risk of appendicular osteoporotic fracture in peri- and postmenopausal women. Annual Meeting, Society for Epidemiologic Research, 1989.

A-34. Stegman MR, Heaney RP, Recker RR, Davies KM, Kelsey WP. Risk of osteoporotic related fracture in a cohort of peri- and postmenopausal women. J Bone Miner Res 4:S170, 1989.

A-35. Lappe JM, Stegman MR, Heaney RP, Recker RR, Davies KM, Ryan RA. Stability as a predictor of osteoporotic fracture syndrome. J Bone Miner Res 4:S190, 1989.

A-36. Brandenburger G, Avioli LV, Chesnut CH III, Heaney RP, Recker RR, Turner C. Ultrasound velocity assessment of bone fragility: methods to achieve accuracy and reproducibility. J Bone Miner Res 4:S231, 1989.

Page 7

A-37. Barger-Lux MJ, Heaney RP, Stegman MR. Effects of moderate caffeine intake on the calcium economy of premenopausal women. J Bone Miner Res 4:S235, 1989.

A-38. Heaney RP. Estrogen-calcium interactions in the postmenopause. J Bone Miner Res 4:S235, 1989.

A-39. Recker RR, Davies KM, Kimmel DB, Heaney RP. Cross-sectional studies overestimate agerelated bone loss. J Bone Miner Res 4:S327, 1989.

A-40. Davies KM, Recker RR, Stegman MR, Heaney RP, Kimmel DB, Leist J. Third decade bone gain in women. J Bone Miner Res 4:S327, 1989.

A-41. Matkovic V, Heaney RP, Chesnut CH III. Absorption of calcium in adolescent females. J Bone Miner Res 4:S381, 1989.

A-42. Weaver CM, Heaney RP. Isotopic exchange of calcium between labeled sources. FASEB 4:A775, 1990.

A-43. Heaney RP. Computing calcium intakes to achieve desired absorptive goals. J Bone Miner Res 5:S111, 1990.

A-44. Davies KM, Recker RR, Heaney RP. Revised criteria for vertebral deformity. J Bone Miner Res 5:S117, 1990.

A-45. Barger-Lux MJ, Heaney RP. Differences in response to calcium infusion in calciumrestricted and calcium-supplemented subjects. J Bone Miner Res 5:S117, 1990.

A-46. Lappe JM, Stegman MR, Heaney RP, Recker RR. Ethnic background as a predictor of osteoporotic fracture syndrome. J Bone Miner Res 5:S118, 1990.

A-47. Stegman MR, Heaney RP, Recker RR. Early bone mineral measurement. A predictor of later appendicular fracture. J Bone Miner Res 5:S117, 1990.

A-48. Avioli LV, Chesnut CH, Brandenburger GH, Heaney RP, Recker RR. Preliminary results from a longitudinal clinical study of ultrasound velocity. J Bone Miner Res 5:S181, 1990.

A-49. Weaver CM, Heaney RP, Martin BR. Effect of seed phytate content on calcium absorption. FASEB 5(4):A560, 1991.

A-50. Weaver CM, Heaney RP, Martin BR, Fitzsimmons ML. Calcium absorption from wheat products. Food Technol, 1991.

A-51. Stegman MR, Heaney RP, Recker RR, Davis KM, Ryan RA. The risk of osteoporotic fracture at age 70 based on a single bone mineral content measurement at age 50. J Soc Epidemiol Res, 1991.

A-52. Kimmel DB, Heaney RP, Avioli LV, Chesnut CH, Recker RR, Lappe JM, Brandenburger GH. Patellar ultrasound velocity in osteoporotic and normal subjects of equal forearm or spinal bone density. J Bone Miner Res 6:S175, 1991.

A-53. Barger-Lux MJ, Heaney RP, Packard PT, Lappe JM, Recker RR. Nutritional correlates of low calcium intake. J Bone Miner Res 6:S164, 1991.

A-54. Matkovic V, Heaney RP. Calcium balance during human growth. Evidence for threshold behavior. J Bone Miner Res 6:S128, 1991.

A-55. Davies KM, Recker RR, Heaney RP, Stegman MR. Healthy women don't shrink. J Bone

Page 8

Miner Res 6:S164, 1991.

A-56. Stegman MR, Heaney RP, Recker RR, Davis KM, Ryan RA. Case-control vs. cohort investigation of the relation between bone mineral content and osteoporotic fracture. J Bone Miner Res 6:S276, 1991.

A-57. Heaney RP, Weaver CM. Effect of plant constituents on food calcium absorbability. J Bone Miner Res 7:S136, 1992.

A-58. Barger-Lux MJ, Heaney RP, Davies KM. Use of the regression discontinuity design in a clinical trial of calcium efficacy. J Bone Miner Res 7:S189, 1992.

A-59. Lappe JM, Heaney RP, Recker RR, Ryan RA. Radiogrammetry as method to predict osteoporotic fractures. J Bone Miner Res 7:S329, 1992.

A-60. Stegman MR, Heaney RP, Recker RR, Leist J, Travers-Gustafson D. Ultrasound measurement of bone quality of a stratified sample of a rural population. J Bone Miner Res 7:S190, 1992.

A-61. Jelic T, Wardlaw GM, Ilich JZ, Andon MB, Smith KT, Heaney RP, Matkovic V. Timing of peak bone mass in Caucasian females. J Bone Miner Res 7:S139, 1992.

A-62. Stegman MR, Heaney RP, Recker RR, Leist J, Travers-Gustafson D. Distribution of bone quality in a rural population. Am J Epidemiol, 1994.

A-63. Heaney RP, Weaver CM. Oxalate in vegetables. Effect on calcium absorbability. J Bone Miner Res 8:S333, 1993.

A-64. Stegman MR, Travers-Gustafson D, Leist J, Heaney RP, Recker RR. Comparison of bone quality of volunteers to randomly sampled study participants. J Bone Miner Res 8:S336, 1993.

A-65. Barger-Lux MJ, Heaney RP, Lanspa SJ, DeLuca HL. Bases of calcium absorptive variability. J Bone Miner Res 8:S338, 1993.

A-66. Boxerman S, Repa-Eschen L, Hunt AH, Anderson JJB, Heaney RP, Leboff MS, Licata A, Lindsay R, Avioli LV. Quantitative assessment of risk factors as determinants of peak bone mass in a healthy, premenopausal population. J Bone Miner Res 8:S258, 1993.

A-67. Travers-Gustafson D, Stegman MR, Leist J, Heaney RP, Recker RR. Comparison of bone quality of volunteers to randomly sampled study participants. Am J Public Health, 1994.

A-68. Heaney RP. The bone remodeling transient: Implications for the design and interpretation of clinical trials. J Bone Miner Res 9:S149, 1994.

A-69. Stegman MR, Heaney RP, Travers-Gustafson D, Barger-Lux MJ. Sonic velocity in cortical bone detects bony fragility. J Bone Miner Res 9:S272, 1994.

A-70. Stegman MR, Travers-Gustafson D, Heaney RP, Recker RR. Comparison of ultrasound and SPA for determining odds ratio of low-trauma fracture in postmenopausal women. J Bone Miner Res 9:S329, 1994.

A-71. Travers-Gustafson D, Stegman MR, Recker RR, Heaney RP. Ultrasound and SPA differences for older women and men with and without a history of low-trauma fracture. J Bone Miner Res 9:S205, 1994.

A-72. Stegman MR, Heaney RP, Recker RR, Davies KM. Differences in estimates of odds of

Page 9

fracture due to misclassification bias. Am J Epidemiol, 1995.

A-73. Packard PT, Weaver CM, Heaney RP. Absorbability of calcium from calcium sulfate, a fortificant. Proceedings IFT Annual Meeting, Book of Abstracts, p. 239, 1995.

A-74. Johnson ML, Gong G, Kimmel DB, Barger-Lux MJ, Heaney RP, Lappe JM, Recker RR. Lack of correlation between parathyroid hormone gene alleles and skeletal phenotype. J Bone Miner Res 10:S367, 1995.

A-75. Barger-Lux MJ, Heaney RP, Davies KM, Johnson ML, Gong G. Vitamin D receptor (VDR) gene polymorphism: relationship to adult bone expansion, bone loss, and body size, in longitudinal data. J Bone Miner Res 10:S184, 1995.

A-76. Heaney RP, Barger-Lux MJ, Davies KM, Ryan RA, Recker RR. Determinants of skeletal size and change with age: a longitudinal study. J Bone Miner Res 10:S246, 1995.

A-77. Travers-Gustafson D, Stegman MR, Heaney RP, Recker RR. The Saunders County Bone Quality Study: bone quality, mass, and other fracture risk factors. J Bone Miner Res 10:S261, 1995.

A-78. Stegman MR, Davies KM, Heaney RP, Recker RR, Lappe JM. The association of patellar ultrasound transmission and forearm densitometry with vertebral fracture; number and severity: The Saunders County Bone Quality Study. J Bone Miner Res 10:S262, 1995.

A-79. Davies KM, Heaney RP. Vertebral shape stability through menopause. J Bone Miner Res 10:S262, 1995.

A-80. Sevcik A, Stegman MR, Davies KM, Heaney RP, Recker RR. Prevalence of vertebral fractures in older women and men: The Saunders County Bone Quality Study. J Bone Miner Res 10:S262, 1995.

A-81. Gong G, Johnson ML, Barger-Lux MJ, Heaney RP, Kimmel DB, Recker RR. Association of PTH gene polymorphism with metacarpal diameter and rate of change in upper radius in women. J Bone Miner Res 10:S462, 1995.

A-82. Packard P, Heaney RP, Recker RR. Serum 25-hydroxyvitamin D levels and milk intake in free-living older women. J Bone Miner Res 11:S317, 1996.

A-83. Stegman MR, Heaney RP, Recker RR, Davies KM, Travers-Gustafson D. Which fractures should be used in the calculation of odds ratios? J Bone Miner Res 11:S353, 1996.

A-84. Davies KM, Heaney RP, Ryan RA. Height loss in older women. J Bone Miner Res 11:S357, 1996.

A-85. Travers-Gustafson D, Stegman MR, Heaney RP, Recker RR. Percent of bone change per year: the Saunders County Bone Quality Study. J Bone Miner Res 11:S359, 1996.

A-86. Barger-Lux MJ, Heaney RP, Dowell S, Bierman J. Relative molar potency of 25hydroxyvitamin D indicates a major role in calcium absorption. J Bone Miner Res 11:S423, 1996.

A-87. Heaney RP, Draper MW. Raloxifene mimics estrogen in human bone remodeling kinetics. J Bone Miner Res 11:S446, 1996.

A-88. Heaney RP, Draper MW. Raloxifene HCl and estrogen: Comparative bone remodeling kinetics. Book of Abstracts 79th Annual Meeting of the Endocrine Society, 1997.

A-89. Günther T, Dawson-Hughes B, Heaney RP, Barrett-Connor E, Lindsay R. Bone mineral

content and density in Caucasian American females. J Bone Miner Res 12:S382, 1997.

A-90. Freeman SPHT, Allen LH, Siekmann JH, Waterman J, Heaney RP. The detection in archived human samples of inadvertently administered ⁴¹Ca tracer. J Bone Miner Res 12:S225, 1997.

A-91. Barger-Lux MJ, Heaney RP, Dowell S, Bierman J. Serum and urine effects of graded oral dosing with vitamin D_3 , 25(OH)D, and 1,25(OH)₂D for short treatment periods. J Bone Miner Res 12:S217, 1997.

A-92. Stegman MR, Davies KM, Heaney RP, Travers-Gustafson D. Percent change and cumulative estimates of forearm mass and density for women and men: The Saunders County Bone Quality Study. J Bone Miner Res 12:S245, 1997.

A-93. Zmuda JM, Cauley JA, Ensrud KE, Heaney RP, Eisman JA, Cummings SR. Vitamin D receptor gene polymorphisms and fractional calcium absorption in older women. J Bone Miner Res 12:S371, 1997.

A-94. Wolf RL, Cauley JA, Danielson ME, Zmuda JM, Charron M, Heaney RP. Calcium absorption does not differ between older African American and Caucasian American women. J Bone Miner Res 12:S140, 1997.

A-95. Danielson ME, Cauley JA, Zmuda JM, Ngo D, Charron M, Heaney RP. Fractional calcium absorption is correlated in mothers and daughters. J Bone Miner Res 12:S491, 1997.

A-96. Ensrud KE, Gore R, Cauley JA, Heaney RP, Cummings SR. Fractional calcium absorption and fracture risk in older women: a prospective study. Bone 23:S151, 1998.

A-97. Recker RR, Davies KM, Dowd RM, Heaney RP. Bone saving effects of low dose continuous estrogen/progestin with calcium and vitamin D in elderly women: a randomized, controlled trial. Bone 23:S158, 1998.

A-98. Wolf RL, Cauley JA, Baker CE, Ferrell RE, Charron M, Caggiula AW, Salamone LM, Heaney RP, Kuller LH. What's good for your heart and colon may not be so good for your bones: low fat, high fiber diet linked to poor calcium absorption. Bone 23:S170, 1998.

A-99. Freeman SPHT, Bierman J, Heaney RP. Measurements of historically calcium isotope labeled subjects indicate the age of the resorbing skeleton. Bone 23:S606, 1998.

A-100. Barger-Lux, MJ, Heaney RP, Davies KM, Ryan RA. Osteoporotic fractures occur among premenopausal women. Bone 23:S621, 1998.

A-101. Iwaniec UT, Shearon CC, Heaney RP, Cullen DM, Yee JA. Leptin increases number of mineralized bone nodules *in vitro*. Bone 23:S212, 1998.

A-102. Stegman MR, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Patellar ultrasound and radius BMC predict low trauma and vertebral incident fracture. Bone 23:S384, 1998.

A-103. McCarron DA, Heaney RP, Dawson-Hughes B. Increased milk intake improves indices of bone health in an older population. FASEB J 13:A581, 1999.

A-104. Heaney RP, Weaver CM. Absorbability of calcium carbonate from various food matrices. FASEB J 13:____, 1999.

A-105. Wolf RL, Zmuda JM, Charron M, Heaney RP, Cauley JA. Calcium absorption efficiency in older men: relationships to age and bone loss. J Bone Miner Res 14:S181, 1999.

Page 11

A-106. Danielson ME, Cauley JA, Charron M, Heaney RP. Is fractional calcium absorption related to postmenopausal bone loss? J Bone Miner Res 14:S521, 1999.

A-107. Barger-Lux MJ, Heaney RP, Davies KM, Chin BK. Bone mass before and after full-term pregnancy in young women with histories of dietary calcium deficiency. J Bone Miner Res 14:S393, 1999.

A-108. Davies KM, Heaney RP, Ryan RA. Elderly height change and HRT use. J Bone Miner Res 14:S384, 1999.

A-109. Deng H-W, Chen W-M, Recker S, Stegman MR, Li J-L, Davies KM, Zhou Y, Deng H-Y, Heaney RP, Recker RR. Direct evidence of genetic determination of osteoporotic fractures. J Bone Miner Res 14:S175, 1999.

A-110. Heaney RP. Sources of bone fragility. Osteoporosis Int 11 (Suppl 2):S43, 2000.

A-111. Heaney RP. Nutrition – Beyond calcium. NIH Consensus Development Conference on Osteoporosis. Book of Program and Abstracts, 33-35, 2000.

A-112. Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MJ, Rafferty K, Hinders S. Calcium intake and healthy weight. J Bone Miner Res 15:S238, 2000.

A-113. Barger-Lux MJ, Heaney RP, Chin B. Seasonal changes in sun exposure at temperate latitudes do not produce measurable differences in calcium absorption efficiency or urinary calcium excretion. J Bone Miner Res 15:S425, 2000.

A-114. Heaney RP, Dowell MS, Bendich A. Bioavailability and the optimization of calcium supplementation. Osteoporos Int 11:(Suppl 5);S7, 2000.

A-115. Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. The magnitude of the PTH response to calcium supplementation. Bone 28(5):S232, 2001.

A-116. Heaney RP. The importance of calcium and vitamin D to bone health throughout life. Bone 28(5):S253, 2001.

A-117. Heaney RP, Barger-Lux MJ, Davies KM, Chen TC, Holick MF. Vitamin D dose response relationships. J Bone Miner Res 16:(Suppl 1);S146, 2001.

A-118. Barger-Lux MJ, Davies KM, Heaney RP, Chin BK, Rafferty K. Calcium supplementation may attenuate accumulation of fat in young women. J Bone Miner Res 16:(Suppl 1);S219, 2001.

A-119. Davies KM, Heaney RP, Ryan R, Rafferty K. Mid-life muscle mass decrease. J Bone Miner Res 16:(Suppl 1);S273, 2001.

A-120. Recker RR, Johnson ML, Davies KM, Recker SM, Heaney RP. Autosomal dominant high bone mass: the phenotype. J Bone Miner Res 16:(Suppl 1);S470, 2001.

A-121. O'Connell M, Madden DM, Murray AM, Heaney RP. Effect of proton pump inhibition on calcium carbonate absorption. J Am Geriatric Soc 50(4):S8, 2002.

A-122. Griffin IJ, Abrams SA, Hicks PD, Heaney RP. Non-digestible oligosaccharides (NDO) increases calcium absorption, especially those whose calcium absorption is poorest. Pediatr Res 51:188A, 2002.

A-123. Davies KM, Heaney RP, Rafferty K. Dietary potassium conserves calcium after menopause. J Bone Miner Res 17 (Suppl 1):S476, 2002.

Page 12

A-124. Heaney RP, Barger-Lux MJ. Not all calcium carbonate supplements are equally absorbable. J Bone Miner Res 17 (Suppl 1):S371, 2002.

A-125. Barger-Lux MJ, Heaney RP, Chen TC, Holick MF. Daily skin dose of vitamin D_3 in healthy men with intensive summer sun exposure. J Bone Miner Res 17 (Suppl 1):S496, 2002.

A-126. Heaney RP. Measuring calcium absorption by pharmacokinetic methods. J Am Coll Nutr 21(5):478, 2002.

A-127. Heaney RP, Bendich A. Effects of vitamin D status on calcium absorptive performance in elderly women. J Am Coll Nutr 21(5):478, 2002.

A-128. Bendich A, Hale CA, Heaney RP. Vitamin D status affects calcium absorptive performance in postmenopausal women. FASEB J 17:A704, 2003.

A-129. Barger-Lux MJ, Auberry-Adams L, Lappe JM, Recker RR, Heaney RP. Towards quantifying the relationship of constitutive skin color to daily skin dose of vitamin D_3 in healthy adults with ample summer sun exposure. J Bone Miner Res 18 (Suppl 2):S180, 2003.

A-130. Recker RR, Lappe JM, Davies KM, Heaney RP. Transmenopausal changes in activation frequency. J Bone Miner Res 18 (Suppl 2): S298, 2003.

A-131. Haynatzki GR, Stegman MR, Davies KM, Lappe JM, Travers-Gustafson D, Heaney RP, Recker RR. Predictors of incident vertebral fractures in men and women. J Bone Miner Res 18 (Suppl 2):S360, 2003.

A-132. Lappe JM, Barger-Lux MJ, Haynatzki G, Heaney RP, Recker RR, Travers-Gustafson D. Body fat is inversely associated with 25-hydroxyvitamin D levels in healthy postmenopausal women. J Bone Miner Res 18 (Suppl 2):S179, 2003.

A-133. Travers-Gustafson D, Lappe JM, Haynatzki G, Heaney RP, Recker RR. Does use of electronic monitoring increase pill taking compliance? J Bone Miner Res 18 (Suppl 2):S271, 2003.

A-134. Armas LAG, Heaney RP, Hollis BW. Vitamin D_2 is much less effective than vitamin D_3 in humans. Abstract OR22-2, p. 103, ENDO 2004 Program and Abstract book, 2004.

A-135. Barger-Lux MJ, Dowell MS, Heaney RP. A relationship between body composition and calcium absorption efficiency. J Bone Miner Res 19(Suppl 1):S302, 2004.

A-136. Heaney RP, Valent DJ, Barton IP. Risedronate protects skeletal mass during intercurrent illness. (Abstract #P167) Calcif Tissue Int 74(Suppl 1):S88, 2004.

A-137. Heaney RP. Bone quality: Shifting the paradigm. European Calcified Tissue Society, Lilly Symposium, "Evolving Perspectives in Osteoporosis Treatment", p. 6, 2004.

A-138. Heaney RP. Promises and perils of the widespread use of DXA for assessment of fracture risk. Abstract #22, p. 14, Bone Quality Meeting Program and Abstract book, 2005.

A-139. Heaney RP, Magowan S, Zhou X, Boonen S. Low calcium intake in postmenopausal women: a review of Phase III trials. Menopause (in presss) 2005.

A-140. Chow WY, Heaney RP. Underutilization of calcium in an osteoporotic population. J Bone Miner Res 20(Suppl 1):S377, 2005.

A-141. Heaney RP, Magowan S, Zhou X, Boonen S. Prevalence of low calcium intake in postmenopausal osteoporotic women: the need for supplementation. J Bone Miner Res 20(Suppl

Page 13

1):S378, 2005.

A-142. Lappe JM, Travers-Gustafson D, Barger-Lux MJ, Davies KM, Heaney RP, Recker RR. Population-based evidence that serum 25(OH)D levels below 80 nmol/L reflect vitamin D deficiency. J Bone Miner Res 20(Suppl 1):S379, 2005.

A-143. Armas LAG, Heaney RP, Barger-Lux MJ. The effects of UV-B light on serum 25(OH)D in humans. J Bone Miner Res 20(Suppl 1):S188, 2005.

A-144. Armas LAG, Heaney RP, Barger-Lux MJ, Huerter C, Lund R. The effects of UV-B light on serum 25(OH)D in humans with dark skin tones. J Bone Miner Res 21 (Suppl 1):S449, 2006.

PUBLICATIONS

ORIGINAL SCIENTIFIC PAPERS

S-1. Heaney RP, Eliel LP. Metabolic and cytochemical changes produced by 6-mercaptopurine in human acute leukemia. Cancer 9:252-61, 1956.

S-2. Heaney RP, Whedon GD. Impairment of hepatic bromsulphthalein clearance by two 17-substituted testosterones. J Lab Clin Med 52:169-175, 1958.

S-3. Heaney RP, Whedon GD. Radiocalcium studies of bone formation rate in human metabolic bone disease. J Clin Endocrinol Metab 18:1246-1267, 1958.

S-4. Heaney RP. Radiocalcium metabolism in disuse osteoporosis in man. Am J Med 33:188-200, 1962.

S-5. Heaney RP. Evaluation and interpretation of calcium kinetic data in man. Clin Orthop 31:153-183, 1963.

S-6. Heaney RP, Bauer GCH, Bronner F, Dymling JF, Lafferty FW, Nordin, BEC, Rich C. A normal reference standard for radiocalcium turnover and excretion in humans. J Lab Clin Med 64:21-28, 1964.

S-7. Heaney RP, Skillman TG. Secretion and excretion of calcium by the human gastrointestinal tract. J Lab Clin Med 64:29-41, 1964.

S-8. Heaney RP. A unified concept of osteoporosis. Am J Med 39:877-880, 1965.

S-9. Rich C, Bernstein DS, Gates S, Heaney RP, Johnston, CC, Rosenberg CA, Schnaper HW, Tewksbury RB, Williams GA. Factors involved in an objective study of the efficacy of treatment of osteoporosis. Clin Orthop 45:63-66, 1966.

S-10. Harris WH, Heaney RP. The effect of growth hormone on skeletal metabolism. Nature 223:403-404, 1969.

S-11. Sullivan JF, Heaney RP. Zinc metabolism in alcoholic liver disease. Am J Clin Nutr 23:170-177, 1970.

S-12. Heaney RP, Suchy N, Sullivan JF. Determination of the endogenous component of alimentary lipemia. J Clin Endocrinol Metab 31:640-646, 1970.

S-13. Riggs BL, Marshall JH, Jowsey J, Heaney RP, Bassingthwaight, JB. Quantitative ⁴⁵Ca autoradiography of human bone. J Lab Clin Med 78:585-598, 1971.

S-14. Heaney RP, Skillman TG. Calcium metabolism in normal human pregnancy. J Clin Endocrinol Metab 33:661-670, 1971.

S-15. Szymendera J, Heaney RP, Saville PD. Intestinal calcium absorption: Concurrent use of oral and intravenous tracers and calculation by the inverse convolution method. J Lab Clin Med 79:570-578, 1972.

S-16. Harris WH, Heaney RP, Jowsey J, Cockin J, Akins C, Graham J, Weinberg EH. Growth hormone: The effect on skeletal renewal in the adult dog, I. Morphometric studies. Calcif Tissue Res 10:1-13, 1972.

Page 15

S-17. Heaney RP, Harris WH, Cockin J, Weinberg EH. Growth hormone: The effect on skeletal renewal in the adult dog, II. Mineral kinetic studies. Calcif Tissue Res 10:14-22, 1972.

S-18. Heaney RP. Whole-body counting: Analysis of retention data for isotopes having prominent fecal excretion. J Lab Clin Med 84:1-5, 1974.

S-19. Recker RR, Saville PD, Heaney RP. Interrelations between 17 ketosteroids, 17 ketogenic steroids, body weight, and height in normal and obese women. Nebr Med J 59:231-235, 1974.

S-20. Heaney RP, Saville PD, Recker RR. Calcium absorption as a function of calcium intake. J Lab Clin Med 85:881-890, 1975.

S-21. Saville PD, Heaney RP, Recker RR. Radiogrammetry at four bone sites in normal middleaged women: Their relation to each other, to calcium metabolism and to other biological variables. Clin Orthop 114:307-315, 1976.

S-22. Harris WH, Heaney RP, Davis LA, Weinberg EH, Coutts RD, Schiller AL. Stimulation of bone formation in vivo by phosphate supplementation. Calcif Tissue Res 22:85-98, 1976.

S-23. Heaney RP, Recker RR, Saville PD. Calcium balance and calcium requirements in middleaged women. Am J Clin Nutr 30:1603-1611, 1977.

S-24. Recker RR, Saville PD, Heaney RP. The effect of estrogens and calcium carbonate on bone loss in postmenopausal women. Ann Intern Med 87:649-655, 1977.

S-25. Heaney RP, Recker RR, Saville PD. Menopausal changes in bone remodeling. J Lab Clin Med 92:964-970, 1978.

S-26. Heaney RP, Recker RR, Saville PD. Menopausal changes in calcium balance performance. J Lab Clin Med 92:953-963, 1978.

S-27. Heaney RP, Recker RR. Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. J Lab Clin Med 99:46-55, 1982.

S-28. Heaney RP. Calcium intake requirement and bone mass in the elderly. J Lab Clin Med 100:309-312, 1982.

S-29. Recker RR, Heaney RP. The effect of milk supplements on calcium metabolism, bone metabolism and calcium balance. Am J Clin Nutr 41:254-263, 1985.

S-30. Elias C, Heaney RP, Recker RR. Placebo therapy for postmenopausal osteoporosis. Calcif Tissue Int 37:6-13, 1985.

S-31. Heaney RP, Recker RR. Estimation of true calcium absorption. Ann Int Med 103:516-521, 1985. (See also, E-7.)

S-32. Heaney RP, Recker RR. Distribution of calcium absorption in middle-aged women. Am J Clin Nutr 43:299-305, 1986.

S-33. Nottestad SY, Baumel JJ, Kimmel DB, Recker RR, Heaney RP. The proportion of trabecular bone in human vertebrae. J Bone Miner Res 2:221-229, 1987.

S-34. Heaney RP, Recker RR. Calcium supplements: anion effects. Bone Miner 2:433-439, 1987.

S-35. Smith KT, Heaney RP, Flora L, Hinders S. Calcium absorption from a new calcium delivery system (CCM). Calcif Tissue Int 42:351-352, 1987.

S-36. Heaney RP, Recker RR, Hinders SM. Variability of calcium absorption. Am J Clin Nutr 47:262-264, 1988.

S-37. Recker RR, Bammi A, Barger-Lux MJ, Heaney RP. Calcium absorbability from milk products, an imitation milk, and calcium carbonate. Am J Clin Nutr 47:93-95, 1988.

S-38. Heaney RP, Weaver CM, Recker RR. Calcium absorbability from spinach. Am J Clin Nutr 47(4):707-709, 1988.

S-39. Heaney RP, Smith KT, Recker RR, Hinders SM. Meal effects on calcium absorption. Am J Clin Nutr 49:372-376, 1989.

S-40. Heaney RP, Avioli LV, Chesnut CH III, Brandenburger GH, Lappe J, Recker RR. Osteoporotic bone fragility. Detection by ultrasound transmission velocity. JAMA 261:2986-2990, 1989.

S-41. Heaney RP, Weaver CM. Oxalate: Effect on calcium absorption. Am J Clin Nutr 50:830-832, 1989.

S-42. Barger-Lux MJ, Heaney RP, Recker RR. Time course of calcium absorption in humans: evidence for a colonic component. Calcif Tissue Int 44:308-311, 1989.

S-43. Davies KM, Recker RR, Heaney RP. Normal vertebral dimensions and normal variation in serial measurements of vertebrae. J Bone Miner Res 4:341-349, 1989.

S-44. Heaney RP, Baylink DJ, Johnston CC Jr, Melton LJ III, Meunier P, Murray TM, Nagant de Deuxchaisnes C. Fluoride therapy for vertebral crush fracture syndrome: status report 1988. Annals Int Med 111(8):678-680, 1989.

S-45. Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. J Bone Miner Res 4:469-475, 1989.

S-46. Davies KM, Recker RR, Stegman MR, Heaney RP, Kimmel DB, Leist J. Third decade bone gain in women. Proceedings ICCRH-ASBMR Joint Meeting, pp. 497-501; Montreal, Quebec, Sept. 9-14, 1989, Elsevier Scientific Publishers.

S-47. Heaney RP. Osteoporotic Fracture Space: An Hypothesis. Bone Miner 6:1-13, 1989.

S-48. Heaney RP, Weaver CM. Calcium absorption from kale. Am J Clin Nutr 51:656-657, 1990.

S-49. Heaney RP. Estrogen-calcium interactions in the postmenopause: a quantitative description. Bone Miner 11:67-84, 1990.

S-50. Heaney RP, Davies KM, Recker RR, Packard PT. Long-term consistency of nutrient intakes. J Nutr 120:869-875, 1990.

S-51. Heaney RP, Recker RR, Weaver CM. Absorbability of calcium sources: the limited role of solubility. Calcif Tissue Int 46:300-304, 1990.

S-52. Barger-Lux MJ, Heaney RP, Stegman MR. Effects of moderate caffeine intake on the calcium economy of premenopausal women. Am J Clin Nutr 52:722-725, 1990.

S-53. Heaney RP, Weaver CM, Fitzsimmons ML, Recker RR. Calcium absorptive consistency. J Bone Miner Res 11(5):1139-1142, 1990.

S-54. Heaney RP, Weaver CM, Fitzsimmons ML. The influence of calcium load on absorption fraction. J Bone Miner Res 11(5):1135-1138, 1990.

Page 17

S-55. Weaver CM, Heaney RP. Isotopic exchange of ingested calcium between labeled sources. Does dietary calcium form a common absorptive pool? Calcif Tissue Int 49:244-247, 1991.

S-56. Heaney RP, Weaver CM, Fitzsimmons ML. Soybean phytate content: effect on calcium absorption. Am J Clin Nutr 53:745-747, 1991.

S-57. Heaney RP. Fecal calcium density: a measure of calcium compliance. J Bone Miner Res 6:469-471, 1991.

S-58. Weaver CM, Heaney RP, Martin BR, Fitzsimmons ML. Human calcium absorption from whole wheat products. J Nutr 121:1769-1775, 1991.

S-59. Davies KM, Recker RR, Stegman MR, Heaney RP. Tallness vs. shrinkage: are women shrinking with age or growing taller with recent birthdate? J Bone Miner Res 6:1115-1120, 1991.

S-60. Weaver CM, Heaney RP, Martin BR, Fitzsimmons ML. Extrinsic vs. intrinsic labeling of the calcium in whole wheat flour. Am J Clin Nutr 55:452-454, 1992.

S-61. Turner CH, Akhter MP, Heaney RP. The effects of fluoridated water on bone strength. J Orthop Res 10:581-587, 1992.

S-62. Matkovic V, Heaney RP. Calcium balance during human growth. Evidence for threshold behavior. Am J Clin Nutr 55:992-996, 1992.

S-63. Stegman MR, Recker RR, Davies KM, Ryan RA, Heaney RP. Fracture risk as determined by prospective and retrospective study designs. Osteoporosis Int 2:290-297, 1992.

S-64. Barger-Lux MJ, Heaney RP, Packard PT, Lappe JM, Recker RR. Nutritional correlates of low calcium intake. In: Chernoff R (ed) Clinics in Applied Nutrition 2(4):39-44, 1992. Andover Medical Publishers, Reading, MA.

S-65. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA 268:2403-2408, 1992.

S-66. Barger-Lux MJ, Heaney RP. Effects of calcium restriction on metabolic characteristics of premenopausal women. J Clin Endocrinol Metab 76:103-107, 1993.

S-67. Heaney RP, Avioli LV, Chesnut CH III, Lappe JM, Recker RR, Brandenburger, GH. Ultrasound velocity through bone predicts incident vertebral deformity. J Bone Miner Res 10:341-345, 1995.

S-68. Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright, JK, Andon MB, Smith KT, Heaney RP. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. J Clin Invest 93:799-808, 1994.

S-69. Heaney RP, Weaver CM, Hinders SM, Martin B, Packard P. Absorbability of calcium from *Brassica* vegetables: broccoli, boy choy, and kale. J Food Sci 58:1378-1380, 1993.

S-70. Weaver CM, Heaney RP, Proulx WR, Hinders SM, Packard PT. Absorbability of calcium from common beans. J Food Sci 58:1401-1403, 1993.

S-71. Davies KM, Recker RR, and Heaney RP. Revisable criteria for vertebral deformity. Osteoporos Int 3:265-270, 1993.

S-72. Weaver CM, Heaney RP, Teegarden D, Hinders SM. Wheat bran abolishes the inverse relationship between calcium load size and absorption fraction in women. J Nutr 126:303-307,

1996.

S-73. Heaney RP, Recker RR. Determinants of endogenous fecal calcium in healthy women. J Bone Miner Res 9:1621-1627, 1994.

S-74. Heaney RP. Protein intake and the calcium economy. J Am Dietetic Assoc 93:1261-1262, 1993.

S-75. Heaney RP. Is there a role for bone quality in fragility fractures? Calcif Tissue Int 53:S3-S5, 1993.

S-76. Heaney RP. The bone remodeling transient: implications for the interpretation of clinical studies of bone mass change. J Bone Miner Res 9:1515-1523, 1994.

S-77. Heaney RP, Weaver CM. Effect of psyllium on absorption of co-ingested calcium. J Am Geriatrics Society 43:1-3, 1995.

S-78. Heaney RP, Dowell MS. Absorbability of calcium in a high calcium mineral water. Osteoporosis Int 4:323-324, 1994.

S-79. Abrams SA, Yergey AL, Heaney RP. Relationship between balance and dual tracer isotopic measurements of calcium absorption and excretion. J Clin Endocrinol Metab 79:965-969, 1994.

S-80. Stegman MR, Heaney RP, Recker RR, Travers-Gustafson D, Leist J. Velocity of ultrasound and its association with fracture history in a rural population. Am J Epidemiol 139:1027-1034, 1994.

S-81. Barger-Lux MJ, Heaney RP. Caffeine and the calcium economy revisited. Osteoporosis Int 5:97-102, 1995.

S-82. Travers-Gustafson D, Stegman MR, Heaney RP, Recker RR. Ultrasound, densitometry, and extraskeletal appendicular fracture risk factors: A cross-sectional report on the Saunders County Bone Quality Study. Calcif Tissue Int 57:267-271, 1995.

S-83. Stegman MR, Heaney RP, Travers-Gustafson D, Leist J. Cortical ultrasound velocity as an indicator of bone status. Osteoporosis Int 5:349-353, 1995.

S-84. Heaney RP, Saito Y, Orimo H. Effect of caseinphosphopeptide on absorbability of coingested calcium in normal postmenopausal women. J Bone Miner Metab 12:77-81, 1994.

S-85. Barger-Lux MJ, Heaney RP, Lanspa SJ, Healy JC, DeLuca HF. An investigation of sources of variation in calcium absorption efficiency. J Clin Endocrinol Metab 80:406-411, 1995.

S-86. Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, Kimmel DB. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 11:1961-1966, 1996.

S-87. Stegman MR, Heaney RP, Recker RR. Comparison of speed of sound ultrasound with single photon absorptiometry for determining fracture odds ratios. J Bone Miner Res 10:346-352, 1995.

S-88. Davies KM, Stegman MR, Heaney RP, Recker RR. Prevalence and severity of vertebral fracture: The Saunders County Bone Quality Study. Osteoporosis Int 6:160-165, 1996.

S-89. Stegman MR, Davies KM, Heaney RP, Recker, RR, Lappe, JM. The association of patellar ultrasound transmissions and forearm densitometry with vertebral fracture, number, and severity: The Saunders County Bone Quality Study. Osteoporosis Int 6:130-135, 1996.

S-90. Barger-Lux MJ, Heaney RP, Hayes J, DeLuca HF, Johnson ML, Gong G. Vitamin D receptor gene polymorphism, bone mass, body size, and vitamin D receptor density. Calcif Tissue Int 57:161-162, 1995.

S-91. Lappe JM, Recker RR, Malleck MK, Stegman MR, Packard PT, Heaney RP. Patellar ultrasound transmission velocity in healthy children and adolescents. Bone 16:251S-256S, 1995.

S-92. Heaney RP, Barger-Lux MJ, Davies KM, Ryan RA, Johnson ML, Gong G. Bone dimensional change with age: interactions of genetic, hormonal, and body size variables. Osteoporos Int 7:426-431, 1997.

S-93. Heaney RP, Barger-Lux MJ, Dowell MS, Chen TC, Holick MF. Calcium absorptive effects of vitamin D and its major metabolites. J Clin Endocrinol Metab 82:4111-4116, 1997.

S-94. Weaver CM, Heaney RP, Nickel KP, Packard PT. Calcium bioavailability from high oxalate vegetables: Chinese vegetables, sweet potatoes, and rhubarb. J Food Sci 62:524-525, 1997.

S-95. Ott SM, Tucci JR, Heaney RP, Marx SJ. Hypocalciuria and abnormalities in mineral and skeletal homeostasis in patients with celiac sprue without intestinal symptoms. Endocrinol Metab 4:201-206, 1997.

S-96. Heaney RP, Yates AJ, Santora AC II. Bisphosphonate effects and the bone remodeling transient. J Bone Miner Res 12:1143-1151, 1997.

S-97. Heaney RP, Draper MW. Raloxifene and estrogen: comparative bone-remodeling kinetics. J Clin Endocrinol Metab 82:3425-3429, 1997.

S-98. Hanes DA, Weaver CM, Heaney RP, Wastney M. Absorption of calcium oxalate does not require dissociation in rats. J Nutr 129:170-173, 1999.

S-99. Shen X, Weaver CM, Martin BR, Heaney RP. Lignin effect on calcium absorption in rats. J Food Sci 63:165-167, 1998.

S-100. Shen X, Weaver CM, Kempa-Steczko A, Martin BR, Phillippy BQ, Heaney RP. Inositol phosphates affect calcium absorption in rats. J Nutr Biochem 9:298-301, 1998.

S-101. Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporos Int 8:222-230, 1998.

S-102. Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D in elderly women. Annals Int Med 130:897-904, 1999.

S-103. Heaney RP, Recker RR, Ryan RA. Urinary calcium in perimenopausal women: normative values. Osteoporos Int 9:13-18, 1999.

S-104. Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 9:19-23, 1999.

S-105. Gong G, Johnson ML, Barger-Lux MJ, Heaney RP. Association of bone dimensions with a parathyroid hormone gene polymorphism in women. Osteoporos Int 9:307-311, 1999.

S-106. Heaney RP, McCarron DA, Dawson-Hughes B, Oparil S, Berga SL, Stern JS, Barr SI, Rosen CJ. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 99:1228-1233, 1999.

Page 20

S-107. Wolf RL, Cauley JA, Baker C, Ferrell RE, Charron M, Caggiula AW, Salamone LM, Heaney RP, Kuller LH. Factors associated with calcium absorption efficiency in pre- and perimenopausal women. Am J Clin Nutr 72:466-471, 2000.

S-108. Freeman SPHT, Heaney RP. A population with ⁴¹Ca-labelled skeletons. Nature (submitted) 1999.

S-109. Deng H-W, Chen W-M, Recker S, Stegman MR, Li J-L, Davies KM, Zhou Y, Deng H, Heaney RP, Recker RR. Genetic determination of Colles' fracture and differential bone mass in women with and without Colles' fracture. J Bone Miner Res 15:1243-1252, 2000.

S-110. Barr SI, McCarron DA, Heaney RP, Dawson-Hughes B, Berga SL, Stern JS, Oparil S. Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. J Am Diet Assoc 100:810-817, 2000.

S-111. Heaney RP, Dowell MS, Rafferty K, Bierman J. Honey enhances the absorption of coingested calcium. J Food Sci (submitted) 1999.

S-112. Ensrud KE, Duong T, Cauley JA, Heaney RP, Wolf RL, Harris E, Cummings SR. Low fractional calcium absorption increases the risk of hip fracture in women with low calcium intake. Ann Intern Med 132:345-353, 2000.

S-113. Weaver CM, Heaney RP, Connor L, Martin BR, Smith DL, Nielsen S. Bioavailability of calcium from tofu as compared with milk in premenopausal women. J Food Sci 67(8):3144-3147, 2002.

S-114. Heaney RP. Dietary protein and phosphorus do not affect calcium absorption. Am J Clin Nutr 72:758-761, 2000.

S-115. Heaney RP, Dowell MS, Rafferty K, Bierman J. Bioavailability of the calcium in fortified soy imitation milk, with some observations on method. Am J Clin Nutr 71:1166-1169, 2000.

S-116. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. Osteoporos Int 11:533-536, 2000.

S-117. Recker RR, Lappe JM, Davies KM, Heaney RP. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res 15(10):1965-1973, 2000.

S-118. Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MJ, Rafferty K, Hinders S. Calcium intake and body weight. J Clin Endocrinol Metab 85:4635-4638, 2000.

S-119. Davies KM, Heaney RP, Recker RR, Barger-Lux MJ, Lappe JM. Hormones, weight change, and menopause. Int J Obesity 25:874-879, 2001.

S-120. Heaney RP, Rafferty K. Carbonated beverages and urinary calcium excretion. Am J Clin Nutr 74:343-347, 2001.

S-121. Freeman SPHT, Beck B, Bierman JM, Caffee MW, Heaney RP, Holloway L, Marcus R, Southon JR, Vogel JS. The study of skeletal calcium metabolism with ⁴¹Ca and ⁴⁵Ca. Nucl Instr Meth Phys Res 172:930-933, 2000.

S-122. Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr 20(3):239-246, 2001.

S-123. Deng HW, Xu FH, Davies KM, Heaney RP, Recker RR. Difference in bone mineral density, bone mineral content, and bone areal size in fracturing and non-fracturing women, and their

Page 21

interrelationships at the spine and hip. J Bone Miner Metab 20:358-366, 2002.

S-124. Davies KM, Heaney RP, Rafferty K. Decline in muscle mass with age in women: a longitudinal study using an indirect measure. Metabolism 51(7):935-939, 2002.

S-125. Heaney RP, Nordin BEC. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr 21(3):239-244, 2002.

S-126. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 77:204-210, 2003.

S-127. Heaney RP, Rafferty K, Dowell MS. Effect of yogurt on a urinary marker of bone resorption in postmenopausal women. J Am Diet Assoc 102(11):1672-1674, 2002.

S-128. Heaney RP, Zizic TM, Fogelman I, Olszynski WP, Geusens P, Kasibhatia C, Alsayed N, Isaia G, Davie MW, Chesnut CH III. Risedronate reduces the risk of first vertebral fracture in osteoporotic women. Osteoporos Int 13:(6):501-505, 2002.

S-129. Heaney RP, Dowell MS, Wolf RL. Estimation of true calcium absorption in men. Clin Chem 48(5):786-788, 2002.

S-130. Heaney RP, Davies KM, Barger-Lux MJ. Calcium and weight: clinical studies. J Am Coll Nutr 21(2):152S-155S, 2002.

S-131. Martin BR, Weaver CM, Heaney RP, Packard PT, Smith DL. Calcium absorption from three salts and CaSO₄-fortified bread in premenopausal women. J Agric Food Chem 50:3874-3876, 2002.

S-132. Deng HW, Deng XT, Conway T, Xu FH, Heaney RP, Recker RR. Determination of bone size of hip, spine, and wrist in human pedigrees by genetic and lifestyle factors. J Clin Densitom 5(1):45-56, 2002.

S-133. Heaney RP. The basis for the post-parathyroidectomy increase in bone mass. J Bone Miner Res 17 (Suppl 2):N154-N157, 2002.

S-134. Heaney RP. Normalizing calcium intake: projected population effects on body weight. J Nutr 133:268S-270S, 2003.

S-135. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 87(11):4952-4956, 2002.

S-136. Griffin IJ, Hicks PMD, Heaney RP, Abrams SA. Enriched chicory inulin increases calcium absorption mainly in adolescents with lower calcium absorption. Nutr Res 23:901-909, 2003.

S-137. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: A randomized, crossover trial. Am J Med 118:778-781, 2005.

S-138. Heaney RP. Is the paradigm shifting? Bone 33:457-465, 2003.

S-139. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 22(2):142-146, 2003.

S-140. Heaney RP. Quantifying human calcium absorption using pharmacokinetic methods. J Nutr 133:1224-1226, 2003.

Page 22

S-141. Shapiro RS, Heaney RP. Co-dependence of calcium and phosphorus on growth and bone development under conditions of varying deficiency. Bone 32:532-540, 2003.

S-142. Heaney RP. Ethical issues in the design of osteoporosis clinical trials: The state of the question. J Bone Miner Res 18(6):1117-1120, 2003.

S-143. Brody GA, Dickey N, Ellenberg SS, Heaney RP, Levine RJ, O'Brien RL, Purtilo RB, Weijer C. Is the use of placebo controls ethically permissible in clinical trials of agents intended to reduce fractures in osteoporosis? J Bone Miner Res 18(6):1105-1109, 2003.

S-144. Heaney RP. Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr 78(5):912-919, 2003.

S-145. Pazianas M, Butcher GP, Subhani JM, Finch PJ, Ang L, Collins C, Heaney RP, Zaidi M, Maxwell JD. Calcium absorption and bone mineral density in celiacs after long-term treatment with gluten-free diet and adequate calcium intake. Osteoporos Int 16(1):56-63, 2005.

S-146. McCarron DA, Heaney RP. Estimated healthcare savings associated with adequate dairy food intake. Am J Hypertension 17:88-97, 2004.

S-147. Heaney RP, Rafferty K, Bierman J. Not all calcium-fortified beverages are equal. Nutr Today 40(1):39-44, 2005.

S-148. Heaney RP, Abrams SA. Improved estimation of the calcium content of total digestive secretions. J Clin Endocrinol Metab 89:1193-1195, 2004.

S-149. Heaney RP. Phosphorus nutrition and the treatment of osteoporosis. Mayo Clinic Proceedings 79(1):91-97, 2004.

S-150. Recker RR, Lappe JM, Davies KM, Heaney RP. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. J Bone Miner Res 19:1628-1633, 2004.

S-151. Rafferty K, Davies KM, Heaney RP. Potassium intake and the calcium economy. J Am Coll Nutr 24(2):99-106, 2005.

S-152. Davies KM, Rafferty K, Heaney RP. Determinants of endogenous calcium entry into the gut. Am J Clin Nutr 80(4):919-923, 2004.

S-153. Armas LAG, Hollis BW, Heaney RP. Vitamin D_2 is much less effective than vitamin D_3 in humans. J Clin Endocrinol Metab 89:5387-5391, 2004.

S-154. Heaney RP, Rafferty K, Dowell MS, Bierman J. Calcium fortification systems differ in bioavailability. J Am Diet Assoc 105(5):807-809, 2005.

S-155. Heaney RP, Rafferty K, Dowell MS, Bierman J. Intestinal absorption is not improved when vitamin D is co-ingested with a calcium source. Am J Clin Nutr (submitted).

S-156. Heaney RP, Valent D, Barton IP. Hospitalization-related bone loss and the protective effect of risedronate. Osteoporos Int 17(2):212-216, 2006.

S-157. Barger-Lux MJ, Heaney RP. Calcium absorptive efficiency is positively related to body size. J Clin Endocrinol Metab 90:5118-5120, 2005.

S-158. Lappe JM, Davies KM, Recker RR, Heaney RP. Quantitative ultrasound: use in screening for susceptibility to stress fractures in female Army recruits. J Bone Miner Res 20(4):571-578,

2005.

S-159. Barger-Lux MJ, Davies KM, Heaney RP. Calcium supplementation does not augment bone gain in young women consuming moderately low calcium diets. J Nutr 135:2362-2366, 2005.

S-160. Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP. Vitamin D status in a rural postmenopausal female population. J Am Coll Nutr 25(5):395-402, 2006.

S-161. Heaney RP. Absorbability and utility of calcium in mineral water. Am J Clin Nutr 84:371-374, 2006.

S-162. Pieper CF, Colon-Emeric C, Caminis J, Betchyk K, Zhang J, Janning C, Shostak J, LeBoff MS, Heaney RP, Lyles KW. Distribution and correlates of serum 25-hydroxyvitamin D levels in a sample of hip fracture patients. J Am Geriatrics Soc (submitted) 2005.

S-163. Davies KM, Akhter M, Heaney RP. BMC vs. BMD: A relook at clinical measures of bone strength. Bone (submitted) August 2006.

PUBLICATIONS REVIEW ARTICLES

R-1. Heaney RP. Mechanism of action of the oral antidiabetic agents. A review. Nebr Med J 43:485, 1958.

R-2. Harris WH, Heaney RP. Skeletal renewal and metabolic bone disease. N Engl J Med 280:193-202, 253-259, 303-311, 1969.

R-3. Heaney RP. Pathophysiology of osteoporosis, with implications for treatment. Texas Med 70:37-45, 1974.

R-4. Heaney RP. Skeletal remodeling physiology and its relation to metabolic bone disease. NY J Med 75:1656-61, 1975.

R-5. Heaney RP. Nutritional factors in postmenopausal osteoporosis. Roche Laboratories Seminars on Aging, 1981.

R-6. Heaney RP, Gallagher JC, Johnston CC, Neer R, Parfitt AM, Whedon GD. Calcium nutrition and bone health in the elderly. Am J Clin Nutr 36:986-1013, 1982.

R-7. Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. Am J Clin Nutr 36:1014-1031, 1982.

R-8. Heaney RP, Lux MJ. Assessing the patient's risk of osteoporosis. Monograph for Osteoporosis – A Clinician's View for Biomedical Information Corporation, 1984.

R-9. Ray RD, Baylink DJ, Johnston CC, Heaney RP, Raisz LG. Symposium: Osteoporosis Revisited. Cont Orthop 8:127-164, 1984.

R-10. Heaney RP, Barger-Lux MJ. Calcium, bone metabolism, and structural failure. In: Triangle 24:91-100, 1985.

R-11. Heaney RP. Book Review: Bone Miner Res, Annual 2. Ed. WA Peck. The Quarterly Review of Biology 60:255-256, 1985.

R-12. Heaney RP. Calcium, bone health, and osteoporosis. In: Bone Miner Res, Annual IV, pp. 255-301. Ed. WA Peck, Elsevier Science Publishers, Amsterdam, 1986.

R-13. Heaney RP. Osteoporosis – The Need and Opportunity for Calcium Fortification. Cereal Foods World 31:349-353, 1986.

R-14. Heaney RP. Calcium Bioavailability. Contemporary Nutrition 11(8):1986.

R-15. Heaney RP. The role of calcium in prevention and treatment of osteoporosis. Physician and Sportsmedicine 15:83-88, 1987.

R-16. Heaney RP. Qualitative factors in osteoporotic fracture: The state of the question. In: Osteoporosis 1987, pp. 281-287. Eds. C Christiansen, JS Johansen, BJ Riis. Viborg: Norhaven Bogtrykken A/S, 1988.

R-17. Heaney RP. Nutritional considerations in bone health and aging. In: Mineral Homeostasis in the Elderly, pp. 115-126. Alan R. Liss, Inc., New York, 1988.

Page 25

R-18. Heaney RP. Adolescence: A key period for building bone capital. In: L'Alimentation Des Adolescents, pp. 53-60. CIDIL, Paris, 1988.

R-19. Heaney RP. The calcium controversy: A middle ground between the extremes. In: Proceedings of the 1987 Special Topic Conference on Osteoporosis. Public Health Reports S104:36-46, 1989.

R-20. Heaney RP. Osteoporosis – current problems in diagnosis and evaluation. In: The Clinical Impact of Bone and Connective Tissue Markers (Proceedings of Symposium), pp. 279-287. Uppsala, Sweden, June 1988. Eds. E Lindh, JI Thorell. Academic Press Inc., London, 1989.

R-21. Heaney RP. Nutritional factors in causation of osteoporosis. In: Annales Chirurgiae et Gynaecologiae 77:176-179, 1989. (Kuopio International Symposium on Osteoporosis, [Finland 8/88]).

R-22. Heaney RP. Optimizing bone mass in the perimenopause: calcium. In: Clinical Disorders of Bone and Mineral Metabolism, pp. 181-186. (Proceedings of the Laurence and Dorothy Fallis International Symposium, Detroit, May 1988). Eds. M Kleerekoper and SM Krane. Mary Ann Liebert, Inc., New York, 1989.

R-23. Heaney RP. Nutritional factors in bone health in elderly subjects: methodological and contextual problems. Am J Clin Nutr 50:S1181-1189, 1989.

R-24. Heaney RP. Is calcium intake important for maximum bone health? In: Osteo News. Excerpta Medica, Lawrenceville, NJ, 1(3):1989.

R-25. Heaney RP. Calcium intake and bone health. In: Osteo Forum. Excerpta Medica, Amsterdam, 2(3):1989.

R-26. Heaney RP. Calcium supplement preparations. The Medical Letter 31:101-103, 1989.

R-27. Heaney RP. Calcium requirements. In: Proceedings of the Nineteenth Steenbock Symposium "Osteoporosis", pp. 303-311, Madison, WI, June 1989, (HF DeLuca and R Mazess, eds). Elsevier Science Publishers, New York, 1990.

R-28. McCarron DA, Lipkin M, Rivlin RS, Heaney RP. Dietary calcium and chronic diseases. Medical Hypotheses 31:265-273, 1990.

R-29. Heaney RP. Availability of calcium from various sources. Bone Clinical and Biochemical News and Reviews 7:54-56, 1990.

R-30. Nordin BEC, Heaney RP. Calcium supplementation of the diet: justified by present evidence. British Med J 300:1056-1060, 1990.

R-31. Heaney RP. Calcium intake and bone health throughout life. JAMWA 45(3):80-86, 1990.

R-32. Heaney RP. Clinical Update. Article in: The Osteoporosis Report, 1990.

R-33. Heaney RP. Bone health after menopause – is calcium the complete answer? Menopause Management 3:5-8, 1990.

R-34. Heaney RP. Myths and models. In: Osteoporosis 1990, pp. 23-29. Eds. C Christiansen, K Overgaard. Osteopress ApS, Copenhagen, 1990.

R-35. Heaney RP. Calcium supplements: practical considerations. Osteoporos Int 1:65-71, 1991.

R-36. Heaney RP, Barger-Lux MJ. Calcium in nutrition and prevention of disease. In: Food and Page 26 Exhibit 1 Nutrition News 63(2):7-10, 1991.

R-37. Heaney RP. Calcium intake in the osteoporotic fracture context: introduction. Am J Clin Nutr 54:242S-244S, 1991.

R-38. Barger-Lux MJ, Heaney RP. Preventing osteoporosis. Pharmacy Focus 4:1-4, 1991.

R-39. Heaney RP. Lifelong calcium intake and prevention of bone fragility in the aged. Calcif Tissue Int 49:S42-45, 1991.

R-40. Heaney RP. Assessment and consistency of calcium intake. In: Nutritional Aspects of Osteoporosis, (Proceedings of International Symposium on Osteoporosis, Lausanne, May 1991), pp. 99-104. Eds. P Burckhardt, RP Heaney. Serono Symposia Publication Vol. 85, Raven Press, New York, 1991.

R-41. Heaney RP. Human calcium absorptive performance – a review. In: Nutritional Aspects of Osteoporosis, (Proceedings of International Symposium on Osteoporosis, Lausanne, May 1991), pp. 115-123. Eds. P Burckhardt, RP Heaney. Serono Symposia Publication No. 85, Raven Press, New York, 1991.

R-42. Heaney RP, Burckhardt P. Concluding Comments: The impact of nutrition in the epidemiology, the prevention, and the treatment of osteoporosis. In: Nutritional Aspects of Osteoporosis, (Proceedings of International Symposium on Osteoporosis, Lausanne, May 1991), pp. 371-375. Eds. P Burckhardt, RP Heaney. Serono Symposia Publication No. 85, Raven Press, New York, 1991.

R-43. Heaney RP. Effect of calcium on skeletal development, bone loss, and risk of fractures. Am J Med 91:23S-28S, 1991.

R-44. Heaney RP. Calcium in the prevention and treatment of osteoporosis. J Int Med 231:169-180, 1992.

R-45. Heaney RP. Hip fracture. A nutritional perspective. Proceedings of the Society for Experimental Biology and Medicine 200:153-156, 1992. (Proceedings of a conference on molecular and comparative nutrition, Washington, DC, July 1991).

R-46. Heaney RP. Human calcium absorptive performance. In: Proceedings of Symposium on Calcium: Intake, Absorption, and Supplements, Amsterdam, 1992.

R-47. Heaney RP. The natural history of vertebral osteoporosis. Is low bone mass an epiphenomenon? Bone 13:S23-S26, 1992.

R-48. Heaney RP. Nutrition and bone health in an aging population. In: Symposium proceedings "Osteoporosis: For a Nutritional Prevention of Risk?" CERIN, Paris, 1992. pp. 23-34.

R-49. Heaney RP. Calcium intake and bone health in the adult. In: Chernoff R (ed) Clinics in Applied Nutrition 2(4):10-29, 1992. Andover Medical Publishers, Reading, MA.

R-50. Heaney RP. Calcium's role in preventing postmenopausal bone loss. Menopause Management 5:9-13, 1992.

R-51. Heaney RP. Nutritional factors in osteoporosis. Ann Rev Nutr 13:287-316, 1993.

R-52. Heaney RP. Why does bone mass decrease with age and menopause. Proceedings of the 4th International Symposium on Osteoporosis, Hong Kong, March, 1993, pp. 158-159. Eds. C Christiansen, B Riis. Handelstrykkeriet Aalborg Aps, Aalborg, Denmark.

Page 27

R-53. Heaney RP, Barger-Lux MJ. Low calcium intake: the culprit in many chronic diseases. J Dairy Sci 77:1155-1160, 1994.

R-54. Heaney RP. Bone mass, nutrition, and other life-style factors. Am J Med 95:29S-33S, 1993.

R-55. Heaney RP. Osteoporosis – 2044. Osteoporosis Int 4:233-237, 1994.

R-56. Heaney RP, Weaver CM, Barger-Lux J. Food factors influencing calcium availability. In: Nutritional Aspects of Osteoporosis 94, (Proceedings of 2nd International Symposium on Osteoporosis, Lausanne, May 1994), pp. 229-241. Eds. P Burckhardt and RP Heaney. Ares-Serono Symposia, Rome, Italy, 1995.

R-57. Barger-Lux MJ, Heaney RP. Determinants of calcium absorption. In: Nutritional Aspects of Osteoporosis '94, (Proceedings of 2nd International Symposium on Osteoporosis, Lausanne, May 1994), pp. 243-251. Eds. P Burckhardt, RP Heaney. Ares-Serono Symposia, Rome, Italy, 1995.

R-58. Heaney RP, Burckhardt P. Nutrition and bone health (concluding comments): In: Nutritional Aspects of Osteoporosis '94, (Proceedings of 2nd International Symposium on Osteoporosis, Lausanne, May 1994), pp. 419-424. Eds. P Burckhardt, RP Heaney. Ares-Serono Symposia, Rome, Italy, 1995.

R-59. Barger-Lux MJ, Heaney RP. The role of calcium intake in preventing bone fragility, hypertension, and certain cancers. J Nutr 124:1406S-1411S, 1994.

R-60. Heaney RP. Bone mass, nutrition, and other life-style factors. Nutrition Reviews 54(4):S3-S10, 1996.

R-61. Heaney RP. Age considerations in nutrient needs for bone health: older adults. J Am Coll Nutr 15(6):575-578, 1996. (Presentation at 6th Annual Meeting of Nutrition and Bone Health Working Group, 1995 ASBMR Meeting, Baltimore, MD, Sept. 12, 1995.)

R-62. Heaney RP. Osteoporosis Prevention: How much calcium does your patient really need? Consultant August:1097-1100, 1995.

R-63. Heaney RP. Pathophysiology of osteoporosis. In: Symposium on Osteoporosis for The American Journal of Medical Sciences, Watts NB ed., 312(6):251-256, 1996.

R-64. Heaney RP. Calcium and osteoporosis: time to think again. In: Symposium proceedings "Nutrition in the Elderly" CERIN, Paris, 1997, pp. 117-124.

R-65. Packard PT, Heaney RP. Medical nutrition therapy for patients with osteoporosis. J Am Diet Assoc 97:414-417, 1997.

R-66. Glüer C-C for the International Quantitative Ultrasound Consensus Group (includes Heaney RP). Quantitative ultrasound techniques for the assessment of osteoporosis: expert agreement on current status. J Bone Miner Res 12:1280-1288, 1997.

R-67. Heaney RP. Pathophysiology of osteoporosis. Osteoporosis Digest 3:11-13, 1997. PMSI Bugamore, The Netherlands.

R-68. Barger-Lux MJ, Heaney RP. Effects of vitamin D₃, 25(OH)D, and 1,25(OH)₂D on calcium absorption efficiency. In: Nutritional Aspects of Osteoporosis '97, (Proceedings of 3rd International Symposium on Osteoporosis, Lausanne, May 1997), pp 229-236. Eds. P Burckhardt, B Dawson-Hughes, RP Heaney. Serono Symposia, Springer-Verlag, New York, 1998.

Page 28

R-69. Heaney RP. Recommended calcium intakes revisited: round table. In: Nutritional Aspects of Osteoporosis '97, (Proceedings of 3rd International Symposium on Osteoporosis, Lausanne, May 1997), pp 317-325. Eds. P Burckhardt, B Dawson-Hughes, RP Heaney. Serono Symposia, Springer-Verlag, New York, 1998.

R-70. Heaney RP. Skeletal health: the roles of calcium and vitamin D (an evolutionary perspective). Food, Nutrition and Agriculture 20:4-12, 1997.

R-71. Heaney RP. Excess dietary protein may not adversely affect bone. J Nutr 128:1054-1057, 1998.

R-72. Heaney RP. Mineral bioavailability in dairy products. Dialogue 26:10-12, 1998.

R-73. Heaney RP. Prevention of hip fracture with calcium and vitamin D. Medscape Orthopedics & Sports Medicine (issue), 1998;http://www.medscape.com. <u>http://www.medscape.com</u>

R-74. Heaney RP. Calcium, dairy products and osteoporosis. Report developed for International Dairy Federation. Schrezenmeir J, Miller GD, eds. J Am Coll Nutr 19(2):83S-99S, 2000.

R-75. Heaney RP. Pathophysiology of osteoporosis. Endocrinology and Metabolism Clinics of North America 27(2):255-265, 1998.

R-76. Heaney RP. Calcium, bone, and human physiology. OBG Management (Supplement October):2-5, 1998.

R-77. Heaney RP. Mineral bioavailability in dairy products. IDF Bulletin No. 336:41-43, 1998.

R-78. Power ML, Heaney RP, Kalkwarf HJ, Pitkin RM, Repke JT, Tsang RC, Schulkin J. The role of calcium in health and disease. Am J Obstet Gynecol 181:1560-1569, 1999.

R-79. Heaney RP. There should be a dietary guideline for calcium. Am J Clin Nutr 71(3):658-661, 2000.

R-80. Weaver CM, Proulx WR, Heaney RP. Choices for achieving adequate dietary calcium with a vegetarian diet. Am J Clin Nutr 70:543S-548S, 1999.

R-81. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver CM. Peak bone mass. Osteoporos Int 11:985-1009, 2000.

R-82. Heaney RP. Effects of caffeine on bone and the calcium economy. Food Chem Toxicol 40:1263-1270, 2002.

R-83. Heaney RP. Calcium intake and lead absorption. Report developed for Roger L. Carrick, J.D., Preston, Gates, & Ellis, Los Angeles, CA, 1996.

R-84. Heaney RP. AAACa research. Report developed for Andrew J. Lane, Lane Labs, Allendale, NJ, 1999.

R-85. Heaney RP. Bioavailability of dairy and other calcium sources. Report developed for Douglas B. DiRienzo, National Dairy Council, Rosemont, IL 1999.

R-86. Heaney RP. Factors influencing the measurement of bioavailability, taking calcium as a model. (Proceedings LSRO Supplement Meeting, Jan. 2000) J Nutr 131:1344S-1348S, 2001.

R-87. Heaney RP. Calcium needs of the elderly to reduce fracture risk. J Am Coll Nutr 20(2):192S-197S, 2001.

R-88. Heaney RP. Why bones break: approaches to the problem. Menopause Management 10 (Suppl. 1):17-18, 2001.

R-89. Heaney RP, Dawson-Hughes B, Gallagher JC, Marcus R, Nieves, JW. The role of calcium in peri- and postmenopausal women: consensus opinion of The North American Menopause Society. Menopause 8(2):84-95-2001.

R-90. Heaney RP. Ethnicity, bone status, and the calcium requirement. Report for National Dairy Council, July, 2001.

R-91. Heaney RP. Ethnicity, bone status, and the calcium requirement. Nutr Res 22:(1–2):153-178, 2002.

R-92. Heaney RP. Constructive interactions among nutrients and bone-active pharmacologic agents with principal emphasis on calcium, phosphorus, vitamin D and protein. J Am Coll Nutr 20(5):403S-409S, 2001.

R-93. Heaney RP. The bone remodeling transient: interpreting interventions involving bone-related nutrients. Nutr Rev 59(10):327-333, 2001.

R-94. Heaney RP. The importance of calcium intake for lifelong skeletal health. Calcif Tissue Int 70:70-73, 2002.

R-95. Heaney RP. The calcium-phosphate connection. Alternative Therapies in Women's Health 4(10):75-77, 2002.

R-96. Heaney RP. The need for calcium throughout the lifespan. OBG Management (Supplement December):5-7, 2002.

R-97. Heaney RP. Remodeling and skeletal fragility. Osteoporos Int 14(Suppl 5):S12-S15, 2003.

R-98. Heaney RP. Advances in therapy for osteoporosis. Clin Med Res 1(2):93-99, 2003.

R-99. Newmark HL, Heaney RP, Lachance PA. Should calcium and vitamin D be added to the current enrichment program for cereal-grain products? Am J Clin Nutr 80:264-270, 2004.

R-100. Heaney RP. New ways of thinking about osteoporosis. New Developments in Rheumatic Diseases 1(2):1-7, 2003.

R-101. Heaney RP. How does bone support calcium homeostasis. Bone 33:264-268, 2003.

R-102. Heaney RP. New findings in vitamin D deficiency. Osteoporosis Today 3(5):4, 2003.

R-103. Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 80 (Suppl 6):1706S-1709S, 2004.

R-104. Heaney RP. Role of dietary sodium in osteoporosis. J Am Coll Nutr 25:271S-276S, 2006.

R-105. Heaney RP. Serum 25-hydroxyvitamin D and parathyroid hormone exhibit threshold behavior. J Endocrinol Invest 28:180-182, 2005.

R-106. Gaugris S, Heaney RP, Boonen S, Kurth H, Bentkover JD, Sen SS. The prevalence of vitamin D inadequacy among postmenopausal women – a systematic review of literature. Quarterly J Med 98(9):667-676, 2005.

R-107. Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol

30

Biol 97(1-2):13-19, 2005.

R-108. Heaney RP. The challenges of calcium. Functional Foods & Nutraceuticals May:54-58, 2005.

R-100. Heaney RP. Barriers to optimizing vitamin D intake for the elderly. J Nutr 136:1123-1125, 2006.

R-110. Heaney RP. Low calcium intake among African Americans: Effects on bones and body weight. J Nutr 136:1095-1098, 2006.

R-111. Heaney RP, Bachmann GA. Interpreting studies of nutritional prevention. A perspective using calcium as a model. J Women's Health 14(10):990-897, 2005.

R-112. Heaney RP. Alendronate plus cholecalciferol for the treatment of osteoporosis. Women's Health 2(1):23-27, 2006.

R-113. Heaney RP. To D or not to D. BoneKEy-Osteovision 2(6):28-31, 2005.

R-114. Heaney RP, Weaver CM. Newer perspectives on calcium nutrition and bone quality. J Am Coll Nutr 24(6):574S-581S, 2005.

R-115. Heaney RP, Carey R, Harkness L. Roles of vitamin D, n-3 polyunsaturated fatty acid, and soy isoflavones in bone health. J Am Diet Assoc 105:1700-1702, 2005.

R-116. Hathcock JN, Shao A, Vieth R, Heaney RP. Risk assessment for vitamin D. Am J Clin Nutr (in press 2007).

R-117. Heaney RP. Absorbability and utility of calcium in mineral waters. Am J Clin Nutr 84:371-374, 2006.

R-118. Heaney RP. The case for improving vitamin D status. J Steroid Biochem Mol Biol (in press) 2006.

R-119. Heaney RP. Bone health. Am J Clin Nutr (in press) 2006.

R-120. Heaney RP. Vitamin D – The iceberg nutrient. J Musculoskeletal Neuronal Interactions (in press) 2006.

PUBLICATIONS

CHAPTERS, MONOGRAPHS, & SYMPOSIUM VOLUMES

C-1. Heaney RP. Evaluation of calcium kinetics in adult humans. In: Medical Uses of Ca-47, International Atomic Energy Agency, Technical Reports Series, No. 10, Vienna, 1962.

C-2. Heaney RP. Summary of results from clinical studies with radiocalcium. In: Medical Uses of Ca-47, International Atomic Energy Agency, Technical Reports Series, No. 10, Vienna, 1962.

C-3. Heaney RP. Interpretation of calcium kinetic data. In: Dynamic Studies of Metabolic Bone Disease, Eds. Pearson OH and Joplin GF, Blackwell Scientific Publishers, Oxford, 1964.

C-4. Heaney RP. Disuse osteoporosis. In: Dynamic Studies of Metabolic Bone Disease, Eds. Pearson OH, Joplin GF, Blackwell Scientific Publishers, Oxford, 1964.

C-5. Heaney RP. Normal calcium kinetics: Application of a newly derived composite reference standard. In: Medical Uses of Ca-47: Second Panel Report, International Atomic Energy Agency, Technical Reports Series, No. 32, Vienna, 1964.

C-6. Heaney RP. Endogenous fecal calcium. In: Medical Uses of Ca-47: Second Panel Report, International Atomic Energy Agency, Technical Reports Series, No 32, Vienna, 1964.

C-7. Heaney RP. Clinical research: Design and methodology. J Oral Surg 23:355, 1965.

C-8. Heaney RP. Diseases of bone. Cecil-Loeb Textbook of Medicine, 12th Edition, Eds., Beeson and McDermott, WB Saunders Co., Philadelphia, 1967.

C-9. Heaney RP. Interpretation of kinetic studies in disorders of mineralization. In: L'OSTEOMALACIE, Eds. Hioco DJ, Masson and Cie, Paris, 1967.

C-10. Heaney RP. Kinetic studies of calcium in metabolic bone disease. Clin Endocrinol II, Eds. Astwood EB, Cassidy CE. Grune & Stratton, New York, 1968.

C-11. Heaney RP. Osteoporosis. In: Current Diagnosis, Ed. Conn & Conn, W.B. Saunders Co., Philadelphia, 1968.

C-12. Heaney RP. Use of isotope techniques in the evaluation of the divalent ion and bone metabolism in renal failure. Arch Intern Med 124:649-654, 1969.

C-13. Heaney RP. Estrogen effects on the skeleton. In: Metabolic Effects of Gonadal Hormones and Contraceptive Steroids. Eds. Salhanick HA, Kipnis D, Plenum Press, New York, 1969.

C-14. Heaney RP. Unified concept of osteoporosis, a second look. In: Osteoporosis, Ed. Uriel Barzel, Grune & Stratton, New York, 1970.

C-15. Harris WH, Heaney RP. Skeletal Renewal and Metabolic Bone Disease, Little Brown & Co., Boston, 1970.

C-16. Heaney RP. Diseases of bone. In: Cecil-Loeb Textbook of Medicine, 13th Edition, Eds. Beeson & McDermott, WB Saunders Co., Philadelphia, 1971.

C-17. Saville PD, Heaney RP. Treatment of osteoporosis with diphosphonates. Seminars in Drug

Treatment 2(1): 1972.

C-18. Heaney RP, Whedon GD. Bone. Encyclopedia Britannica, 1974.

C-19. Heaney RP. Menopausal effects on calcium homeostasis and skeletal metabolism. In: Menopause and Aging, DHEW Publication, 1973.

C-20. Heaney RP. Calcium tracers in the study of vertebrate calcium metabolism. In: Biological Mineralization, John Wiley & Sons, Inc., New York, 1973.

C-21. Heaney RP. Measurement of skeletal remodeling by means of bone-seeking isotopes. In: Clinical Aspects of Metabolic Bone Disease, Eds. Frame B, Parfitt AM, Duncan H, Excerpta Medica, Amsterdam, 1973.

C-22. Saville PD, Heaney RP. Osteoporosis. In: Practical Geriatrics, Ed. HP von Hahn, Karger, Basel, 1974.

C-23. Heaney RP, Saville PD. Diseases of bone. In: Cecil-Loeb Textbook of Medicine, 14th Edition, Eds. Beeson & McDermott, WB Saunders Co., Philadelphia, 1975.

C-24. Heaney RP. Bone turnover and balance: Comparison of histometric and whole body measures. In: Bone Morphometry. Proc First Workshop Bone Morphometry, Ed. ZFG Jaworski, University of Ottawa Press, 1976.

C-25. Heaney RP. Estrogens and postmenopausal osteoporosis. In: Symposium on Perimenopause, Clinical Obstetrics and Gynecology 19:791-803, 1976.

C-26. Heaney RP. Calcium kinetics in plasma: As they apply to the measurements of bone formation and resorption rates. In: The Biochemistry and Physiology of Bone, Ed. GH Bourne, Academic Press, 1976.

C-27. Heaney RP. Vitamin D and osteoporosis. In: Vitamin D: Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism, Eds. Norman A, Schaefer K, Coburn J, DeLuca H, Fraser D, Grigoleit H, Herrath D. Walter de Gruyter, Inc., Elmsford, New York, 1977.

C-28. Heaney RP. Prevention and care of osteoporosis. In: Improving the Quality of Health Care for the Elderly. Ed. Brookbank J. University Presses of Florida, Gainesville, Florida, 1978.

C-29. Heaney RP. Calcium metabolic changes at menopause. Their possible relationship to postmenopausal osteoporosis. In: Proc of 2nd International Symposium on Osteoporosis. Ed. Barzel U, Grune and Stratton, New York, 1979.

C-30. Heaney RP. Physiological effects of diphosphonate in postmenopausal osteoporosis. Proc International Symposium on Diphosphonate in Therapy. Ed. A Caniggia, Instituto Gentili, Pisa, Italy, 1980.

C-31. Heaney RP, Luby RJ. For women only. In: Better Homes and Gardens After 40, Health and Medical Guide, Ed. Cooley, Meredith Corp. 1980.

C-32. Heaney RP, Recker RR. Osteoporosis-related nutritional influences on bone calcium. In: Osteoporosis: Recent Advances in Pathogenesis and Treatment, Eds. DeLuca, Frost, Jee, Johnston, and Parfitt, University Park Press, 1981.

C-33. Heaney RP. Osteoporosis. In: Disorders of Mineral Metabolism. Eds. Bronner F, Coburn J,

33

Academic Press, New York, 1981.

C-34. Heaney RP. Unified concept of the pathogenesis of osteoporosis: Updated. In: Osteoporosis: Recent Advances in Pathogenesis and Treatment, Eds. DeLuca, Frost, Jee, Johnston, and Parfitt, University Park Press, 1981.

C-35. Recker RR, Heaney RP. Are age-related bone loss and osteoporosis due to a primary defect in bone remodeling? In: Osteoporosis: Recent Advances in Pathogenesis and Treatment, Eds. DeLuca, Frost, Jee, Johnston, and Parfitt, University Park Press, 1981.

C-36. Heaney RP. Nutritional, hormonal, and mechanical factors in age-related bone loss. In: Proceedings of the International Symposium on Osteoporosis, John Wiley & Sons Limited, 1982.

C-37. Baylink DJ, Chesnut CH, Hazzard WR, Heaney RP, Johnston CC, Peck WA, Riggs BL. Treatment of postmenopausal osteoporosis. Proceedings of a symposium held February 1982. A Hahnemann CME Program, TransMedica, Inc., New York, 1982.

C-38. Heaney RP. "The role of diet and activity in the treatment of osteoporosis" in Diet and Exercise: Synergism in Health Maintenance, Eds. Philip L. White and Therese Mondeika. AMA, Chicago, Illinois, 1982.

C-39. Heaney RP. "Osteoporosis", The World Book Encyclopedia, 1983.

C-40. Heaney RP. Determinants of age-related bone loss. In: Clinical Disorders of Bone and Mineral Metabolism, Eds. Frame & Potts, Excerpta Medica International Congress Series 617, 1983.

C-41. Heaney RP. Prevention of age-related osteoporosis in women. In: The Osteoporotic Syndrome. Ed. LV Avioli, Grune & Stratton, New York, 1983.

C-42. Heaney RP. Natural history of osteoporosis. In: Proceedings of the First International Conference on Osteoporosis Social and Clinical Aspects. Florence, Italy; Nov. 1983. Eds. C Gennari, G Segre, Excerpta Medica 1984, 87-93.

C-43. Heaney RP. Risk factors in age-related bone loss and osteoporotic fracture. In: Proceedings of the Copenhagen International Symposium on Osteoporosis. Copenhagen, Denmark; June 1984, 245-251. Eds. C Christiansen, CD Arnaud, BEC Nordin, AM Parfitt, WA Peck, BL Riggs, Dept. of Clinical Chemistry, Glostrup Hospital, Denmark.

C-44. Heaney RP. Calcium balance and calcium requirements in women: prophylactic and therapeutical considerations. In: Selecta (Germany journal) 37:3015, Sept. 1984.

C-45. Heaney RP. The role of calcium in osteoporosis. J Nutr Science and Vitaminology 31:S21-S26, 1985. Proceedings of the International Workshop on Calcium Metabolism and Aging. Tokyo, Japan; Dec. 1984. Center for Academic Publications, Japan.

C-46. Heaney RP. Summary and Prospects. J Nutr Science and Vitaminology 31:S71-S72, 1985. Proceedings of the International Workshop on Calcium Metabolism and Aging. Tokyo, Japan; Dec. 1984. Center for Academic Publications Japan.

C-47. Heaney RP. Les Besoins Calciques A La Peri-Menopause. In: L'Alimentation Des Personnes Agees, Center Interprofessional de Documentation et d'Information Laitieres, pp. 65-

Exhibit 1

34

85, 1985.

C-48. Heaney RP. Hormonal and Dietary Effects on the Skeleton. In: Proceedings of the University of Missouri's 19th Annual Conference on Trace Substances in Environmental Health, pp. 17-20. Ed. Delbert D. Hemphill. University of Missouri, Columbia, Missouri, June 3-6, 1985.

C-49. Heaney RP. Calcium intake, bone health, and aging. In: Nutrition, Aging, and Health, pp. 165-186. Ed. Eleanor A Young. Alan R Liss, Inc., New York, 1986.

C-50. Heaney RP. Osteoporosis. In: MEDICINE for the Practicing Physician, 2nd edition. Chapter 242, pp. 550-552. Ed. J Willis Hurst, Butterworths, Stoneham, Massachusetts, 1988.

C-51. Heaney RP. Prevention of osteoporotic fracture in women. In: The Osteoporotic Syndrome, 2nd Edition, pp. 67-90. Ed. LV Avioli. Grune & Stratton, New York, 1987.

C-52. Heaney RP. The role of nutrition in prevention and management of osteoporosis. In: Clinical Obstetrics & Gynecology 30(4):833-846, 1987, Ed. M. Notelovitz. Harper & Rowe, Philadelphia.

C-53. Heaney

RP. Nutritional factors in bone health. In: Osteoporosis: Etiology, Diagnosis and Management, pp. 359-372. Eds. BL Riggs, LJ Melton III, Raven Press, New York, 1988.

C-54. Heaney RP. High calcium intake is important in preventing osteoporosis in women. In: Debates in Medicine 1988, Vol. 1:166-191, 1988. Ed. Barnes HV. Year Book Medical Publishers.

C-55. Heaney RP, Barger-Lux MJ. Bone up now for stronger bones later. In: The World Book Health and Medical Annual 1989, pp. 56-69. World Book, Inc., Chicago, 1988.

C-56. Recker RR, Heaney RP. Calcium nutrition and its relationship to bone health. In: Nutrition, Aging, and the Elderly, Chap. 8, pp. 183-193. Eds. Munro and Danford, Plenum Publishing Co., New York, 1989.

C-57. Heaney RP. Calcium. In: Progress in Basic and Clinical Pharmacology, Vol. 4: Calcium Metabolism, pp. 28-54. Ed. John Kanis. Karger, Basel, 1990.

C-58. Heaney RP. Calcium and vitamin D in human nutrition. In: Calcium Vitamin D, and Prevention of Colon Cancer, pp. 9-21. Eds. M Lipkin, HL Newmark, & G Kelloff. CRC Press, Boca Raton, FL 1991.

C-59. Whedon GD, Heaney RP. Effects of physical inactivity, paralysis, and weightlessness. In: Bone, Vol. 7, pp. 57-77. Ed. Brian Hall, CRC Press, Boca Raton, 1991.

C-60. Heaney RP. Osteoporosis. In: MEDICINE for the Practicing Physician, 3rd edition. Section 9, Chapter 40, pp. 617-619. Ed. J Willis Hurst, Butterworths, Stoneham, Massachusetts, 1992.

C-61. Heaney RP. Prevention of osteoporotic fracture in women. In: The Osteoporotic Syndrome, 3rd Edition, pp. 89-107. Ed. LV Avioli. Wiley-Liss, Inc., New York, 1993.

C-62. Heaney RP, Matkovic V. Inadequate peak bone mass. In: Osteoporosis: Etiology, Diagnosis and Management, 2nd edition, pp. 115-131. Eds. BL Riggs, LJ Melton III, Lippincott-Raven Publishers, Philadelphia, 1995.

C-63. Heaney RP. Osteoporosis. In: Nutrition in Women's Health. Eds. D. Krummel, P. Kris-Etherton, Aspen Publishers, Gaithersburg, Maryland, pp. 418-439, 1996.

C-64. Heaney RP. Osteoporosis. In: The Cambridge World History of Food. Eds. K.F. Kiple, CK Ornelas-Kiple, Cambridge University Press, New York, New York, pp. 947-960, 2000.

C-65. Heaney RP. Skeletal development and maintenance: the role of calcium and vitamin D. In: Advances in Endocrinology and Metabolism. Ed. R.A. Kreisberg, Mosby, Chicago, IL, 6:17-38, 1995.

C-66. Heaney RP. Osteoporosis. In: Encyclopedia Britannica, Medical and Health Annual, pp. 342-347, 1994.

C-67. Heaney RP. Nutrition and bone mass. In: Physical Medicine and Rehabilitation Clinics of North America. Ed. V. Matkovic, WB Saunders, Philadelphia, PA 6:(3);551-566, 1995.

C-68. Davies KM, Recker RR, Heaney RP. An expert-systems approach to the detection of vertebral deformity. In: Vertebral Fracture in Osteoporosis. Chapter 16, pp. 261-269. Eds. H.K. Genant, M. Jergas, C. van Kuijk. Radiology Research and Education Foundation, San Francisco, 1995.

C-69. Heaney RP. Osteoporosis. In: MEDICINE for the Practicing Physician, 4th edition, pp. 666-669. Ed. J Willis Hurst. ppleton & Lange, Stamford, CT, 1996.

C-70. Heaney RP. Osteoporosis. In: Encyclopedia Britannica, 1997 Medical and Health Annual, pp. 313-316, 1996.

C-71. Heaney RP. Design considerations for osteoporosis trials. In: Osteoporosis, pp. 1125-1142, 1996. Marcus R, Feldman D, Kelsey J, eds. Academic Press, San Diego, CA.

C-72. Heaney RP. Nutrition and risk for osteoporosis. In: Osteoporosis, pp. 483-505, 1996. Marcus R, Feldman D, Kelsey J, eds. Academic Press, San Diego, CA.

C-73. Heaney RP. Pathogenesis of postmenopausal osteoporosis. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Third Edition), pp. 252-256, 1996. Favus M et al., eds. Lippincott-Raven, Philadelphia.

C-74. Heaney RP. Nutrition and osteoporosis. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Third Edition), pp. 262-264, 1996. Favus M et al., eds. Lippincott-Raven, Philadelphia.

C-75. Heaney RP. Calcium. In: Principles of Bone Biology, pp. 1007-1018. Bilezikian JP, Raisz LG, Rodan GA, eds. Academic Press, San Diego, 1996.

C-76. Heaney RP, Bonjour JP. Multifaceted therapy for a multifactorial condition. In: Papapoulos SE et al. (eds) Osteoporosis 1996. Amsterdam: Elsevier Publishers, 1996;287-290.

C-77. Heaney RP. Bone biology in health and disease. In: Modern Nutrition in Health and Disease, 9th edition. Shils ME, Olson JA, Shike M, Ross AC, eds., pp. 1327-1337, 1999. Williams & Wilkins, Baltimore.

C-78. Weaver CM, Heaney RP. Calcium. In: Modern Nutrition in Health and Disease, 9th edition. Shils ME, Olson JA, Shike M, Ross AC, eds., pp. 141-155, 1999. Williams & Wilkins, Baltimore.

36

C-79. Heaney RP. Osteoporosis: Vitamins, minerals, and other micronutrients. In: Preventive Nutrition: The Comprehensive Guide for Health Professionals. Bendich A, Deckelbaum RJ, eds., pp. 285-302, 1997. Humana Press, Inc., Totowa, NJ.

C-80. Heaney RP. Vitamin D: Role in the calcium economy. In: Vitamin D. Feldman D, Glorieux FH, Pike JW, eds., pp. 485-497, 1997. Academic Press, San Diego, CA.

C-81. Heaney RP. Non-pharmacologic prevention of osteoporosis: nutrition and exercise. In: Osteoporosis: Diagnosis and Management. Meunier PJ, ed. Martin Dunitz, London, pp, 161-174, 1997.

C-82. Heaney RP. How to interpret new data. In: Osteoporosis in Clinical Practice: A Practical Guide for Diagnosis and Treatment. Geusens P, ed. Springer-Verlag, London, pp. 175-178, 1997.

C-83. Heaney RP. Pathogenesis of postmenopausal osteoporosis. In: Osteoporosis, Fundamentals of Clinical Practice, pp. 74-76, 1997. Favus M, ed. Lippincott-Raven, Philadelphia.

C-84. Heaney RP. Nutrition and osteoporosis. In: Osteoporosis, Fundamentals of Clinical Practice, pp. 86-88, 1997. Favus M, ed. Lippincott-Raven, Philadelphia.

C-85. Heaney RP. Osteoporosis. In: Textbook of Women's Health, pp. 445-454. Wallis LA, ed. Lippincott-Raven, Philadelphia, 1998.

C-86. Heaney RP. Aging and calcium balance. In: The Aging Skeleton. Rosen C, Glowacki J, Bilezikian JP, eds. Academic Press, San Diego, pp. 19-26, 1999.

C-87. Heaney RP. Nutrition and osteoporosis. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Fourth Edition). Favus M, et al., eds. Lippincott Williams & Wilkins, Philadelphia, pp 270-273, 1999.

C-88. Heaney RP. Trace element and mineral nutrition in skeletal health and disease. In: Clinical Nutrition of the Essential Trace Elements and Minerals, pp. 239-249. Bogden JD and Klevay LM, eds. Humana Press, Totowa, NJ, 2000.

C-89. Heaney RP. Calcium nutriture: a model system for understanding menopause-nutrient interactions. In: Menopause: Biology and Pathobiology, pp. 481-494. Lobo RA, Kelsey J, Marcus R, eds. Academic Press, San Diego, 2000.

C-90. Heaney RP. Osteoporosis: Minerals, vitamins, and other micronutrients, pp. 271-291. In: Preventive Nutrition: The Comprehensive Guide for Health Professionals, 2nd Edition. Bendich A, Deckelbaum RJ, eds. Humana Press, Inc., Totowa, NJ, 2001.

C-91. Heaney RP. Calcium intake and the prevention of chronic disease, pp. 31-50. In: Nutritional Health: Strategies for Disease Prevention. Wilson T and Temple NJ, eds. Humana Press, Totowa, NJ, 2001.

C-92. Heaney RP. Design considerations for clinical investigations of osteoporosis, pp. 513-532. In: Osteoporosis, 2nd Ed, Vol. 2. Marcus R, Kelsey J, Feldman D, eds. Academic Press, San Diego, CA, 2001.

C-93. Heaney RP. Nutrition and risk for osteoporosis, pp. 669-700. In: Osteoporosis, 2nd Ed, Vol. 1. Marcus R, Kelsey J, Feldman D, eds. Academic Press, San Diego, CA, 2001.

C-94. Heaney RP. Dairy foods and osteoporosis, pp. 193-249. In: Handbook of Dairy Foods and

Nutrition, 2nd edition. Miller GD, Jarvis JK, McBean LD, eds. CRC Press, Boca Raton, 2000.

C-95. Weaver CM, Heaney RP. Bone health and the vegetarian, pp. 251-289. In: Handbook of Dairy Foods and Nutrition, 2nd edition. Miller GD, Jarvis JK, McBean LD, eds. CRC Press, Boca Raton, 2000.

C-96. Heaney RP. Calcium metabolism. In: Encyclopedia of Aging, 3rd edition. Maddox GL, ed. Springer, New York, 2001.

C-97. Heaney RP. The dairy controversy: facts, questions, and polemics, pp. 155-164. In: Nutritional Aspects of Osteoporosis '00. Burckhardt P, Dawson-Hughes B, Heaney RP, eds. Academic Press, San Diego, 2001.

C-98. Heaney RP. Calcium, bone, and life. In: Osteoporosis: Pathophysiology and Clinical Management, pp. 265-292. Orwoll ES, Bliziotes M, eds. Humana Press, Totowa, NJ, 2002.

C-99. Heaney RP. Osteoporosis, pp. 653-684. In: Nutrition in the Prevention and Treatment of Disease. Coulston AM, Rock CL, Monsen ER, eds. Academic Press, San Diego, 2001.

C-100. Heaney RP. The role of nutrition in osteoporotic fracture risk, pp. 293-321. In: Osteoporosis. Zanchetta JR, Talbot JR, eds. Panamerica, Buenos Aires, 2001.

C-101. Heaney RP. Calcium. In: Principles of Bone Biology, pp. 1325-1337. Bilezikian JP, Raisz LG, Rodan GA, eds. Academic Press, San Diego, 2002.

C-102. Heaney RP. How to interpret new data. In: Osteoporosis in Daily Clinical Practice: A Guide for Risk Assessment and Treatment, 2nd edition, pp. 213-218, 2004. Geusens P, Lindsay R, Sambrook P, eds. Springer-Verlag, London.

C-103. Heaney RP. Calcium. In: Encyclopedia of Dietary Supplements. Coates PM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, eds. New York: Marcel Dekker, 2005.

C-104. McBean LD, Miller GD, Heaney RP. Effect of cow's milk on human health, pp. 205-221. In: Beverages in Nutrition and Health. Wilson T, Temple NJ, eds. Humana Press, Totowa, NJ, 2004.

C-105. Heaney RP, Weaver CM. Calcium and vitamin D. In: Endocrinol Metab Clin N Am 32(1):181-194, 2003. Bilezikian JP, ed. Elsevier Science, W.B. Saunders Co., Philadelphia, PA.

C-106. Heaney RP. Nutrition and osteoporosis. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Fifth Edition) pp. 352-355. Favus M, Kleerekoper M, Lane N, eds. American Society for Bone and Mineral Research, Washington, DC, 2003.

C-107. Heaney RP. Sodium, potassium, phosphorus, and magnesium, pp. 327-344. In: Nutrition and Bone Health. Holick M, Dawson-Hughes B, eds. Humana Press, Totowa, NJ, 2004.

C-108. Heaney RP. Vitamin D: Role in the calcium economy, 773-787. In: Vitamin D, 2nd edition. Feldman D, Glorieux FH, Pike JW, eds. Academic Press, San Diego, CA, 2005.

C-109. Heaney RP. Serum 25-hydroxy-vitamin D and the health of the calcium economy, pp. 227-244. In: Nutritional Aspects of Osteoporosis, 2nd Edition. Burckhardt P, Dawson-Hughes B, Heaney RP, eds. Elsevier Inc., San Diego, CA, 2004.

C-110. Heaney, RP. Nutrients, interactions, and foods. The Importance of Source, pp. 61-76. In: Nutritional Aspects of Osteoporosis, 2nd Edition. Burckhardt P, Dawson-Hughes B, Heaney RP,

38

eds. Elsevier Inc., San Diego, CA, 2004.

C-111. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Vitamin D Round Table, pp. 263-270. In: Nutritional Aspects of Osteoporosis, 2nd Edition. Burckhardt P, Dawson-Hughes B, Heaney RP, eds. Elsevier Inc., San Diego, CA, 2004.

C-112. Heaney RP. Osteoporosis: Protein, minerals, vitamins, and other micronutrients, pp. 433-460. In: Preventive Nutrition: The Comprehensive Guide for Health Professionals, 3rd Edition. Bendich A, Deckelbaum RJ, eds. Humana Press, Inc., Totowa, NJ, 2005.

C-113. Weaver CM, Heaney RP. Calcium. In: Modern Nutrition in Health and Disease, 10th edition, pp. 194-210. Shils ME, Olson JA, Shike M, Ross AC, eds. Lippincott Williams & Wilkins, Baltimore, 2005.

C-114. Heaney RP. Bone biology in health and disease. In: Modern Nutrition in Health and Disease, 10th edition, pp. 1314-1325. Shils ME, Olson JA, Shike M, Ross AC, eds. Lippincott Williams & Wilkins, Baltimore, 2005.

C-115. Heaney RP. Nutrition and osteoporosis. In: Current Topics in Osteoporosis. Deng HW, ed., pp. 67-117. World Scientific Publication Company, Singapore, 2005.

C-116. Heaney RP. Calcium metabolism. In: Encyclopedia of Aging, 4th edition. Maddox GL, ed. Springer, New York, (in press) 2005.

C-117. Weaver CM, Heaney RP. Introduction, pp. 1-3. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-118. Heaney RP. Bone as the calcium nutrient reserve, pp. 7-12. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-119. Heaney RP. Requirements for what endpoint, pp. 97-104. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-120. Heaney RP. The calcium economy, pp. 145-162. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-121. Heaney RP. Calcium in systemic human health, pp. 313-317. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-122. McCarron D, Heaney RP. Calcium and phosphate control in patients with renal disease, pp. 411-420. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-123. Weaver CM, Heaney RP. Food sources, supplements, and bioavailability, pp. 129-142. In: Calcium in Human Health. Weaver CM, Heaney RP, eds. Humana Press, Totowa, NJ, 2006.

C-124. Heaney RP. Nutrition and osteoporosis. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th edition. Kleerekoper M, Lane N, eds. ASBMR Publications, Washington, DC, (in press) 2006.

C-125. Heaney RP. Calcium intake and disease prevention. In: Brazilian Archives of Endocrinology and Metabolism 50(4):685-693, 2006. Bandeira F, Borges J, Bilezekian JP, eds.

C-126. Heaney RP. Design considerations for clinical investigations of osteoporosis. In: Osteoporosis, 3rd Ed. Marcus R, Feldman D, Nelson D, Rosen C, eds. Elsevier Inc., San Diego,

CA (in press) 2007.

C-127. Heaney RP. Nutrition and risk for osteoporosis. In Osteoporosis, 3rd Ed. Marcus R, Feldman D, Nelson D, Rosen C, eds. Elsevier Inc., San Diego, CA (in press) 2007.

C-128. Heaney RP. Effects of protein on the calcium economy. In: Nutritional Aspects of Osteoporosis. Burckhardt P, Dawson-Hughes B, Heaney RP, eds. Elsevier Inc., Amsterdam, (in press) 2007.

C-129. Heaney RP. Calcium, bone, and life. In: Osteoporosis: Pathophysiology and Clinical Management, 2nd Ed. Adler RAA, ed. Humana Press, Totowa, NJ (in press) 2007.

PUBLICATIONS HIGHER EDUCATION PAPERS

H-1. Heaney RP. Interdisciplinary integration in health sciences curricula. Trans NY Acad Sci 33:324-332, 1974.

H-2. Heaney RP. Podiatric medicine: Its role and function within academic health science centers. J Podiatr Med Educ 6:30-32, 1975.

H-3. Heaney RP. Integration of health professions education. Am J Pharm Educ 39:440-445, 1975.

H-4. Heaney RP. How others view clinical pharmacy – the physician. In: Proc First International Congress on Clinical Pharmacy Education, American Association of Colleges of Pharmacy, Washington, D.C., 1976.

H-5. Heaney RP. Accountability and responsibility of the dental school within the university. J Dent Educ 491:494-498, 1977.

H-6. Heaney RP. The problem of cost in health professions education. J Podiatr Med Educ 8:9-12, 1977.

H-7. Brodie DC, Heaney RP. Need for reform in health professions accrediting. Science, 201:589-593, 1978.

H-8. O'Neill TM, Heaney RP. Accreditation in higher education: Institutional stance: Active or reactive? Prepared for Association of Academic Health Centers, Dec. 1981.

H-9. O'Neill TM, Heaney RP. Taking the initiative in accreditation. Educational Record, 63:57-60, 1982.

H-10. Heaney RP. The Academic Health Center – Promise, Reality, Prospect. "The Academic Health Center Concept" In: Proceedings Symposium, ASCO Annual Meeting, June, 1982.

H-11. Heaney RP. An attack on the cost-structure of health professions education: The view of one chief academic officer. In: Proc Conference on the Study of the Impact of Changes in Federal Policy on Academic Health Centers, pp. 91-97, September, 1982.

H-12. Heaney RP. Past, present, and future of the association. Paradigm shifts in higher education and in health care. In: Proc 1983 Annual Meeting of the Association of Academic Health Centers, Scottsdale, Arizona, September 1983.

H-13. Heaney RP, Barger-Lux MJ. Concepts in crisis: paradigm shifts in higher education and in health care. Educational Record 65:42-47, 1984.

H-14. Heaney RP. The climate of a professional education. Am J Pharmaceutical Education 48:363-366, Winter 1984.

H-15. Heaney RP, Barger-Lux MJ. Priming students to read research critically. Nursing & Health Care, 7(8):421-424, 1986.

41

H-16. Heaney RP, Barger-Lux MJ. The togetherness factor of the academic health center: Is it real? Does it matter? J Prof Nsg 3(1):46-53, 1987.

H-17. Heaney RP. Standards of quality: The path to excellence? Nursing & Health Care 8(4):219-221, 1987.

H-18. Heaney RP, Barger-Lux MJ. Preparing health professionals to be critical consumers of research: A multiprofessional approach. J Health Administration Education 6(1):127-137, 1988.

PUBLICATIONS

MISCELLANEOUS BOOKS AND PAPERS

M-1. Heaney RP. A perspective on the role of drugs in national health policy. Proc of 1st Symposium on Drugs in Saudi Arabia: Appropriate Use of Medicine. Eds., Moustafa, Aboul-Enein, Hamed and Meshal, University of Riyad Press, 1980.

M-2. Heaney RP, Burke EC. The Entrance Rite: Are We Doing it Wrong? Today's Parish, 14:7-9, 1982.

M-3. Heaney RP. Health Facilities Challenged to Uphold Mission Values. Health Progress (special issue) September 1985, pp. 97-101.

M-4. Heaney RP, Dougherty CJ. Research for Health Professionals: Design, Analysis, and Ethics. Creighton University, Varsity Press, 1981, 1986.

M-5. Barger-Lux MJ, Heaney RP. For better and worse: The technological imperative in health care. Social Science and Medicine 22:1313-1320, 1986.

M-6. Heaney RP. What Choice Did He Have? America 155(15):316-320, 1986.

M-7. Heaney RP, Dougherty CJ. Research For Health Professionals: Design, Analysis, and Ethics. Iowa State University Press, 1988.

M-8. Heaney RP, Barger-Lux MJ. Calcium and Common Sense: How to Have Good Bones All Your Life. Ed. J. Duff, Doubleday, New York, 1988.

M-9. Heaney RP. Religion and Science: The Problem That Won't Go Away. Window (Spring):12-15, 1990.

M-10. Heaney RP. RU-486 and Abortion Strategies. America 164:12-13, 1991.

M-11. Heaney RP. Bridging the Rift. Window (Winter):18-20, 1990-91.

M-12. Heaney RP. Does Catholic Medical Education Have a Future? Window (Fall):23-25, 1992.

M-13. Heaney RP. Does Catholic Medical Education Have a Future? Health Progress January-February 1993, p. 67.

M-14. Heaney RP. Sex, Natural Law, and Bread Crumbs. America 170:12-16, 1994.

M-15. Heaney RP. The Intersalt Study Reveals Some Unexpected Connections. America 174:16-20, 1996.

M-16. Prioreschi P, Heaney RP, Brehm E. A quantitative assessment of ancient therapeutics: poppy and pain in the Hippocratic Corpus. Medical Hypotheses 51:325-331, 1998.

M-17. Heaney RP. Foreword for "Quantitative Ultrasound: Assessment of Osteoporosis and Bone Status" edited by Njeh C, Hans D, Glüer C, Fuerst T, Genant H. Martin Dunitz, (in press) 1999.

M-18. Heaney RP. Bone loss and dietary protein. Clinical Pearls News 9:101, 1999.

PUBLICATIONS EDITORIAL COMMENTS

E-1. Heaney RP. Estrogens and osteoporosis (Editorial). West J Med 125:149-150, 1976.

E-2. Heaney RP. Protection against loss of bone and fracture in postmenopausal women. (Correspondence). West J Med 134:74-5, 1981.

E-3. Heaney RP. Research advances and resource constraints. N Engl J Med 305:1352-1353, 1981.

E-4. Heaney RP. Premenopausal Prophylactic Calcium Supplementation, (Questions & Answers). JAMA 245:1362, 1981.

E-5. Heaney RP. Early Postmenopausal Osteoporosis, (Questions & Answers). JAMA 249:90, January 1983.

E-6. Heaney RP. En recherche de la difference (P<.05). Bone Miner 1:99-114, 1986.

E-7. Heaney RP, Recker RR. Estimating true fractional calcium absorption. Ann Int Med 1988;108(6):905-906. (See also, S-31.)

E-8. Heaney RP, Ryan RA. Relationship between measured and recalled body height. N Engl J Med 319:795, 1988.

E-9 Heaney RP. Reply to W Harris. Am J Clin Nutr 48:1518, 1988.

E-10. Heaney RP. Calcium Absorption. J Bone Miner Res 4:795-796, 1989.

E-11. Recker RR, Heaney RP. Age-related bone loss. J Bone Miner Res 5:307-308, 1990.

E-12. Heaney RP. Bone mass and osteoporotic fractures. Calcif Tissue Int 47:63-65, 1990.

E-13. Recker RR, Heaney RP. Response to Doctors Ross and Rozenberg. J Bone Miner Res 5:1274, 1990.

E-14. Heaney RP. Osteoporosis made easy. J Am Geriatric Society 38:1159-1160, 1990.

E-15. Avioli LV, Heaney RP. Calcium intake and bone health. Calcif Tissue Int 48:221-223, 1991.

E-16. Heaney RP. Osteoporosis at the end of the century. Western J Med 154:106-107, 1991.

E-17. Heaney RP. ⁴⁷Ca Alert. J Bone Miner Res 6:99, 1991; Calcif Tissue Int 48:1991.

E-18. Heaney RP. How do we know what we know? The randomized controlled trial revisited. J Bone Miner Res 6:103-105, 1991.

E-19. Heaney RP. How can we tell if a treatment works? Further thoughts on the randomized controlled trial. Osteoporos Int 1:215-217, 1991.

E-20. Heaney RP. Is a dissolution standard for calcium supplements necessary? Calcif Tissue Int 50:197, 1992.

E-21. Heaney RP. Calcium intake and chronic disease. In: Chernoff R (ed) Clinics in Applied Nutrition 2(4):1-2, 1992. Andover Medical Publishers, Reading, MA.

E-22. Heaney RP. Lost sampling units and investigational power. J Bone Miner Res 7:1119-1121, 1992.

E-23. Heaney RP. Musculoskeletal Q&A. Bone density measurements a crude management tool in osteoporosis. J Musculoskel Med 9:12, 1992.

E-24. Heaney RP. Thinking straight about calcium. N Engl J Med 328:503-505, 1993.

E-25. Heaney RP. More thoughts on hospital malnutrition: 'the skeleton in the closet'. J Am Diet Assoc 93:400, 1993.

E-26. Heaney RP. SI units and common sense. Am J Clin Nutr 57:948, 1993.

E-27. Heaney RP. What shall we take for our null hypothesis? Osteoporos Int (submitted) 1993.

E-28. Heaney RP. Fluoride and osteoporosis. Ann Int Med 120:689-690, 1994.

E-29. Heaney RP. Nutrient interactions and the calcium requirement. J Lab Clin Med 124:15-16, 1994.

E-30. Heaney RP. Interpreting trials of bone active agents. Am J Med 98:329-330, 1995.

E-31. Heaney RP. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. J Bone Miner Res 10:172, 1995.

E-32. Heaney RP. Optimal calcium intake. JAMA 274:1012, 1995.

E-33. Heaney RP. Bone mass, the mechanostat, and ethnic differences. J Clin Endocrinol Metab 80:2289-2290, 1995.

E-34. Heaney RP. Calcium, parathyroid function, bone, and aging. J Clin Endocrinol Metab 81:1697-1698, 1996.

E-35. Heaney RP, Kanis JA. The interpretation and utility of ultrasound measurements of bone. Bone 18:491-492, 1996.

E-36. Heaney RP. Some questions about epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. Am J Epidemiol 145:858-859, 1997.

E-37. Heaney RP. Food: what a surprise! Am J Clin Nutr 64:791-792, 1996.

E-38. Barr SI, Heaney RP. Changes in bone mineral density in male athletes. JAMA 277:22-23, 1997.

E-39. Heaney RP. Nutrition: a whole organism science. Nutrition 13:689-690, 1997.

E-40. Heaney RP. Nutrient effects: Discrepancy between data from controlled trials and observational studies. Bone 21:469-471, 1997.

E-41. Heaney RP. Calcium intake and kidney stones in women. Ann Intern Med 127:846, 1997.

E-42. Sørensen OH, Nielsen SP, Charles P, Eriksen EF, Mosekilde L, Heaney RP, Falch J, Halse J, Haug E. Consensus development statement on osteoporosis. Osteoporos Int 7:589, 1997.

E-43. Heaney RP. Bone mass, bone loss, and osteoporosis. Ann Intern Med 128:313-314, 1998.

E-44. Heaney RP. Nutrition and catch-up bone augmentation in young women. Am J Clin Nutr 68:523-524, 1998.

E-45. Heaney RP. Whole organism physiology and ethnic differences in bone. J Lab Clin Med 132:358-359, 1998.

E-46. Heaney RP. Bone mass, bone fragility, and the decision to treat. JAMA 280:2119-2120, 1998.

E-47. Heaney RP. Lessons for nutritional science from vitamin D. Am J Clin Nutr 69:825-826, 1999.

E-48. Heaney RP. Absorbing calcium. Clin Chem 45:161-162, 1999.

E-49. Heaney RP. Age-related osteoporosis in Chinese women. Am J Clin Nutr 69:1291-1292, 1999.

E-50. Heaney RP. Commentary on Khovidhunkit & Shoback, Clinical effects of raloxifene hydrochloride in women. JAMA Women's Health Information Center, 1999.

E-51. Heaney RP, Weaver CM. Bioavailability testing with tracer labeling. Food Product Design, November 1999.

E-52. Heaney RP. Vitamin D: How much do we need, and how much is too much? Osteoporos Int 11:553-555, 2000.

E-53. Heaney RP. Is calcium citrate superior as a calcium supplement? No. Point/Counterpoint in Physician's Weekly, Jan. 17, 2000.

E-54. Heaney RP. Calcium supplement bioequivalence. J Clin Pharmacol (submitted 12/99).

E-55. Heaney RP. Meta-analysis of calcium bioavailability. Am J Therapeutics 8(1):73-74, 2000.

E-56. Heaney RP. The skeletal response to estrogen. Metabolism 49(8):1083-1084, 2000.

E-57. Heaney RP. More evidence and still no action. J Clin Endocrinol Metab 85(9):3009-3010, 2000.

E-58. Heaney RP. Diversity, quotas, and the ethics of clinical research. N Engl J Med (submitted 7/12/00).

E-59. Heaney RP. Lead in calcium supplements – cause for alarm or celebration? JAMA 284:1432-1433, 2000.

E-60. Heaney RP, Berner B, Louie-Helm J. Dosing regimen for calcium supplementation. J Bone Miner Res 15(11):2291, 2000.

E-61. Heaney RP. Protein intake and bone health: the influence of belief systems on the conduct of nutritional science. Am J Clin Nutr 73:5-6, 2001.

E-62. Heaney RP, Dowell MS, Bierman J. Comment on the use of the term "intrinsic labeling". Am J Clin Nutr 73:128-129, 2001.

E-63. Weaver CM, Heaney RP. Dairy consumption and bone health. Am J Clin Nutr 73:660, 2001.

E-64. Heaney RP. Reply to JE Kerstetter et al. Am J Clin Nutr 73:991-992, 2001.

E-65. Heaney RP. Letter to Editor – Soy vs. cow milk. Dietitian's Edge 2(3):15, 2001.

E-66. Recker RR, Heaney RP. The role of combination treatment for osteoporosis. J Clin Endocrinol Metab 86(5):1888-1889, 2001.

E-67. Heaney RP. Reply to A. Sebastian et al. Am J Clin Nutr 74:412, 2001.

E-68. Recker RR, Lappe JM, Davies KM, Heaney RP. Perimenopausal bone loss: principally due to estrogen depletion. J Bone Miner Res 16:2367, 2001.

E-69 Heaney RP. Protein and Calcium – Antagonists or Synergists? Am J Clin Nutr 75(4):609-610, 2002.

E-70. Melton LJ III, Heaney RP. Too much medicine? Or too little? Bone 32(4):327-331, 2003.

E-71. Heaney RP, Recker RR, Lappe JM. Effects of calcium supplementation on serum lipid levels in postmenopausal women. Am J Med 114(7):620-621, 2003.

E-72. Heaney RP. Bone mineral content, not bone mineral density, is the correct bone measure for growth studies. Am J Clin Nutr 78:350-351, 2003.

E-73. Heaney RP. Sensitivity of parathyroid hormone response to calcium intake. Am J Clin Nutr 78:493, 2003.

E-74. Heaney RP. Vitamin D depletion and effective calcium absorption. J Bone Miner Res 18(3):1342, 2003.

E-75. Heaney RP. Blood lead levels and hypertension. JAMA 290:460-461, 2003.

E-76. Fitzpatrick L, Heaney RP. Got soda? Bone Miner Res 18(9):1570-1572, 2003.

E-77. Heaney RP. Low-calcium diet. Can Med Assoc J 169(6):542, 2003.

E-78. Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. J Clin Endocrinol Metab 88(11):5107-5108, 2003.

E-79. Heaney RP. Measuring bone mass accumulation. Am J Clin Nutr 79(2):341, 2004.

E-80. Heaney RP, Fitzpatrick L. The soda debate fizzes on. J Bone Miner Res 19(3):522, 2004.

E-81. Heaney RP, Fitzpatrick L. Soda isn't only low in calcium. J Bone Miner Res 19(5):872, 2004.

E-82. Heaney RP. Research and public health implications of the intricate relationship between calcium and vitamin D in the prevention of colorectal neoplasia. J Natl Cancer Inst 96(10):805-806, 2004.

E-83. Heaney RP. Measuring calcium absorption. Am J Clin Nutr 81(6):1451, 2005.

E-84. Heaney RP. BMD: The problem. Osteoporos Int 16(9):1013-1015, 2005.

E-85. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 16(7):713-716, 2005.

E-86. Rafferty K, Davies KM, Heaney RP. Potassium absorption from meat, dairy, and cereals is highly efficient. JADA (in press) 2005.

E-87. Heaney RP, Rafferty K, Davies KM. Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women. J Clin Endocrinol Metab 90(7):4417, 2005.

E-88. Heaney RP, Recker RR. Combination and sequential therapy for osteoporosis. N Engl J Med 353:624-625, 2005.

E-89. Heaney RP. Measuring what isn't there. Clin Chem 51:2003-2004, 2005.

E-90. Recker RR, Lappe JM, Davies KM, Heaney RP. Bone remodeling: biochemical markers or bone biopsy? J Bone Miner Res 21(1):180, 2006.

E-91. Heaney RP, Rafferty K. Assessing nutritional quality. Am J Clin Nutr 83:722-723, 2006.

E-92. Heaney RP. Nutrition and chronic disease. Mayo Clinic Proceedings 81(3):297-299, 2006.

E-93. Heaney RP. Milk is one of best sources of many nutrients. Chicago Tribune, Editorial, Feb. 18, 2006.

E-94. Heaney RP, Rafferty K. The settling problem. J Am Diet Assoc (in press) Nov. 2006.

E-95. Heaney RP. Nutrition, chronic disease, and the problem of proof. Am J Clin Nutr 84:471-472, 2006.

E-96. Newmark HL, Heaney RP. Commentary: Calcium, vitamin D, and risk of colorectal cancer. Nutr Cancer (in press) 2006.

E-97. Heaney RP. EMB and Common Sense: Practical and ethical issues in clinical trials for osteoporosis. "Perspective" in Future Rheumatology (in press) 12/2006.

E-97. Heaney RP, Weaver CM. Comment on Winzenberg article. BMJ on-line Rapid Responses 9/26/06.

PUBLICATIONS LETTERS/BOOK REVIEWS

L-1. Heaney RP. Nuclear Arms. "Another Point of View" in Omaha World-Herald, August 1983.

L-2. Heaney RP. Medical Resources in the Event of a Nuclear War. "Another Point of View" in Omaha World-Herald, June 1984.

L-3. Heaney RP. Nuclear Disarmament. "Letter to the Editor", The Catholic Voice, November 1984.

L-4. Heaney RP. The Academic Health Center – In Memoriam. "Another Point of View" in Omaha World-Herald, July 1985.

L-5. Heaney RP. Hospitals and the Poor. "Another Point of View" in Omaha World-Herald, November 1985.

L-6. Heaney RP. Why Britain Can't Afford Informed Consent – A Dissenting View. "Letters" in The Hastings Center Report, 16:45, 1986.

L-7. Heaney RP. Medicine is Chancy. "Correspondence" in Commonweal, Vol. CXIII, p. 130, March 14, 1986.

L-8. Heaney RP. The Dubious Morality of Intercollegiate Athletics. "Another Point of View" in Omaha World-Herald, March 1986.

L-9. Heaney RP. Pope's Action Must Be Resisted. "Another Point of View" in Omaha World-Herald, September 16, 1986.

L-10. Heaney RP. Protest at Offutt – Criticism misses the point. "Letter to the Editor", The Catholic Voice, April 8, 1988.

L-11. Heaney RP. Unity in ritual. "Correspondence" in Commonweal, Vol. CXV, p. 642, December 2, 1988.

L-12. Heaney RP. Daly's Professorship. National Catholic Reporter, p. 20, May 26, 1989.

L-13. Heaney RP. A Horse is a Horse. National Catholic Reporter, p. 21, September 22, 1989.

L-14. Heaney RP. Weigh all medical evidence. "Another Point of View" in Omaha World-Herald, January 31, 1990.

L-15. Heaney RP. Not even an option for some. America 164:386, 1991.

L-16. Heaney RP. USDA Pyramid Deserved Stillbirth. "Another Point of View" in Omaha World-Herald, May 5, 1991.

L-17. Heaney RP. Food Processors Should Create Calcium-Fortified Products. "Another Point of View" in Omaha World-Herald, October 27, 1991.

L-18. Heaney RP. Guidelines Proposed for Health-Care Solution. "Another Point of View" in

Omaha World-Herald, April 13, 1992.

L-19. Heaney RP. Milk Message Bad for Our Bones. "Another Point of View" in Omaha World-Herald, April 18, 1995.

L-20. Heaney RP. What is Sokolof Agenda? "Public Pulse", Omaha World-Herald, June 7, 1995.

L-21. Heaney RP. Jumping to Conclusions on Milk. "Voice of the People" in Chicago Tribune, March 21, 1996.

L-22. Heaney RP. Thermodynamics. "Letter to Editor" Window Magazine, Spring, 1996, p. 25.

L-23. Heaney RP. Physicians Committee Cloaks Real Agenda. "Commentary". Omaha World-Herald, December 21, 1999.

L-24. Heaney RP. The Faces Behind Us. America 183:18-20, 2000.

L-25. Heaney RP. Life and Death. The Next 100 Years in Biomedical Sciences. Creighton University Magazine, Spring 2001, pp.32-38.

L-26. Heaney RP. (Book Review) Calcium Hunger: Behavioral and Biological Regulation by Jay Schulkin. N Engl J Med Aug. 16, 2001.

L-27. Heaney RP. Terrorism left nation leery of remote risk. Omaha World-Herald, January 28, 2002.

L-28. Heaney RP. Chance, God, and the Economy. Creighton University Magazine, pp. 30-33, Summer 2002.

L-29. Heaney RP. Excessive regulation imposes a heavy cost. "Midlands Voices" of Omaha World-Herald, January 13, 2003.

L-30. Heaney RP. Why nutrition doesn't make it onto medicine's radar screen. Creighton University Magazine, page 55, Summer 2003.

L-31. Heaney RP. The need for conversion. Commonweal CXXX(15):44-45, 2003.

L-32. Heaney RP. Catholic annulment is not mere divorce. "Midlands Voices" of Omaha World-Herald, January 7, 2004.

L-33. Heaney RP. Why the Catholic Church is a lucrative target. "Midlands Voices" of Omaha World-Herald, March 3, 2004.

L-34. Heaney RP. Patterns of complicity. Acumen J Life Sciences March 2004.

L-35. Heaney RP. Judge whether drugs help more than harm. "Midlands Voices" of Omaha World-Herald, January 21, 2005.

L-36. Heaney RP. Defensive reading 101: How to be a good consumer of medical news. Creighton University magazine, pp. 19-21, Spring 2005.

L-37. Heaney RP. On calcium studies. "Public Pulse" of Omaha World-Herald, February 27. 2006.

L-38. Heaney RP. Schools looking good. "Public Pulse" of Omaha World-Herald, May 22, 2006.

Exhibit 2

[]	Page	Study/ Article	Journal
	LL652	"Title 21-FOOD AND DRUGS: CHAPTER 1- FOOD AND DRUG ADMINISTRATIO N, DEPARTMENT OF HEALTH AND HUMAN SERVICES- CONTINUED: PART 101 FOOD LABELING-Table of Contents: Subpart E-Specific Requirements for Health Claims." 1999. Sec. 101.72 Health Claims: Calcium and Osteoporosis	
2	LL653- LL663	AAA Calcium- Collected Data." 3ACalcium Inc., from Fujix Inc. Contains Charts	

3	LL664- LL666	Effect of Calcium Supplement-action of Bone Density and Parathyroid Function in Elderly Subjects (Fujita, et al.,1995)	Mineral and Electrolyt e Metabolis m, 1995
4	LL667- LL671	Heated Oyster Shell Seaweed Calcium (AAA Ca) on Osteoporosis (Fujita, et al., 1996)	Calcified Tissue Internatio nal, 1995
5	LL672- LL675	A three-year comparative trial in osteoporosis treatment: Effect of combined alfacalcidol and elcatonin (Fujita, et al.)	Mineral Metabolis m, 1997

6	LL676-	Peripheral	Journal of
	LL679	computed	Bone and
		tomography (pQCT)	Mineral
		detected short-term	Metabolis
		effect of AAACa	m, 2000
		(heated oyster shell	3
		with HAI)	
7	LL680-	"Osteoporosis:	Osteoporo
	LL684.	Past, Present and	sis
		Future." T. Fujita.	Internatio
			nal, 1997
		1	1

			T T D
8	LL685-	"Increase of	Journal of
	LL689.	intestinal calcium	Bone and
-)	absorption and bone	
		mineral density by	Metabolis
		heated algal	m, 2000
		ingredient (HAI) in	
		rats." Takuo Fujita,	
		Yoshio Fujii,	
		Bunrei Goto,	
		Akimitsu Miyauchi,	
		Yasuyuki Takagi,	<u> </u>
		Shinsaku	
	2	Kobayashi, Katsuo	
		Kamoshita, Naoji	
		Mikuni, Yokiko	
		Kurihara, and Ikumi	
		Shikauchi.	

9	LL690-	"Effects of Active	Journal of
	LL695.	Amino Acid	Bone and
		Calcium: Its	Mineral
		Bioavailability on	Metabolis
		Intestinal	m, 1998
		Absorption,	
		Osteoporosis and	
	:	Removal of	
		Plutonium in	
		Animals." Satoshi	
		Fukada.	
10	LL696-	"Osteoporosis in	Calcium
	LL703.	Asia." Takuo Fujita	, Research
		M.D.	Institute,
			Kishiwada
			, Japan
11	LL704-	"Calcium	Journal of
11			Bone and
	LL707.	supplementation	Mineral
		and parathyroid	
		hormone." Shigeki	Metabolis
		Ohgitani, Yoshio	m. (1998)
		Fujii, and Takuo	
		Fujita.	

12	LL708-	"Calcium and	Calcium
	731.	Osteoporosis."	Research
		Takuo Fujita.	Institute,
			Osaka,
			Japan
13	LL732	"Calcium	Abstract
		supplementation	from the
		reduces vertebral	Journal of
		bone loss in per	Clinical
		menopausal women:	Endocrino
		a controlled trial in	l Metab.
		248 women	1991.
		between 46 and 55	
		years of age." P.J.	
		Elders, et al.	;
		Lidois, et di	
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14	LL733	Letter to Mr.	
14	دد ا باب	Andrew J. Lane.	
		Takuo Fujita, M.D.	
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15	LL734	"Effect of heated	World
		oyster shell with	Congress
		algal ingredient	on
	2	(Adva-Cal) on	Osteoporo
		osteoporosis." T	sis 2000.
		Fujita, et al.	
		5	
16	LL735-	Letter to Mr. Andy	Asian
	LL749	Lane with abstracts.	Pacific
		Takuo Fujita, M.D.	Congress
			of Bone
			Morphom
			etry
	· · · ·		
			<u> </u>

17	LL750-	"Reappraisal of	Journal of
	LL756	Katsuragi Calcium	Bone and
		study, a prospective,	Mineral
		double-blind,	Metabolis
		placebo-controlled	m, 2004
		study of the effect	
:		of active absorbable	
		algal calcium (AAA	
		Ca) on vertebral	
		deformity and fracture." Takuo	
		Fujita, et al.	<i>.</i>
	:		
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18	LL757-	"Active Absorbable	Clinical
	LL764	Algal Calcium	Calcium,
		(AAA Ca) Changes	2005
		Calcium Paradigm.'	'
		Takuo Fujita.	
		1 -	
1			

19	LL765	"Please Note: Several Other Studies on AAACa Calcium (AdvaCAL) Published in Japanese are available but not included in the binder. They are available upon request."	
20	LL766- LL773	"An interview with Takuo Fujita, M.D."	
21	LL774- LL792	"Product and Marketing Analysis- -Calcium Supplements." Monica Reinagel (Consultant)	Lane Labs (2001)

22		Period.' " Bone and Joint Health .	Bone and Joint Health
23	LL794- LL795	"The effect of calcium citrate on bone density in the early and mid- postmenopausal period: a randomized placebo controlled study." L.A. Ruml, et, al.	American J There. 1999.

LL796	"Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals." L Strause, et,al.	Journal Nutrition. 1994.
LL797- LL801	"Comparison of the Treatment Effects of Ossein- Hydroxyapatite Compound and Calcium Carbonate in Osteoporotic Females." P. Rüegsegger, et, al.	Osteoporo sis Internatio nal. 1995.
	LL797-	LL797- LL797- "Comparison of the LL801 "Comparison of the Treatment Effects of Ossein- Hydroxyapatite Compound and Calcium Carbonate in Osteoporotic Females." P.

26	LL802.	"Assessment of	PubMed
20	1-002.	osteoporosis:	1997
		comparison of	1777
		-	
		radiographic	
		absorptiometry of	
		the phalanges and	-
		dual X-ray	
		absorptiometry of	
		the radius and	
		lumbar spine." M	
		Takada, et, al.	
27	LL803-	"Correcting calcium	Journal of
	LL804.	nutritional	Bone
		deficiency prevents	Mineral
		spine fractures in	Research.
		elderly women." RR	1996.
		Recker, et, at.	
	1		

28	LL805-	"EFFECT OF	The New
	LL811	CALCIUM AND	England
÷		VITAMIN D	Journal of
		SUPPLEMENTATI	Medicine.
		ON ON BONE	1997.
		DENSITY IN MEN	
		AND WOMEN 65	
		YEARS OF AGE	
		OR OLDER." Bess	
		Dawson Huges,	
		M.D.; Susan S.	
		Harris, et, al.	

29	LL812-	Effects of Calcium	Osteoporo
	LL819.	Supplements on	sis
		Femoral Bone	Internatio
		Mineral Density	nal. 1994.
		and Vertebral	
		Fracture Rate in	
		Vitamin-D-Replete	
	•	Elderly Patients." T	
		Chevalley, et, al.	
30	LL820.	"Osteoporosis and	Disease
50		Calcium."	States.
			1994.
			17771

	LL826.	EFFECT OF	England Journal of Medicine.
32	LL827- LL829.	"Bioavailability and Clinical Uses of Calcium Salts." Charles Y.C. Pak, M.D.	CRN Annual Scientific Sessions 1988
33	LL830	"Re: Dr. Lane in Osaka." PretiumGrp. Email. 1999.	

34	LL831.	Letter to Monica	:
51		Reinagel. Oakford	
		Bain. August 17,	
		2001.	
		2001.	
	-		
	* .		
35	LL832-	"CALCIUM	Osteoporo
	LL833.	SUPPLEMENTATI	s Int
		ON TO LOWER	
		PARATHYROID	
		HORMONE."	
		SLT@mail.nerac.co	4
	·	m. 2001.	
		III. 2001.	
36	LL834-	"CALCIUM	Arzneimit
	LL835	SUPPLEMENTATI	tel-
		ON TO LOWER	Forschung
		PARATHYROID	2001.
		HORMONE."	
		SLT@mail.nerac.co	
		m.	
	-		

37	LL837.	"A randomized controlled trial of vitamin D supplementation on preventing postmenopausal bone loss and modifying bone metabolism using identical twin pairs." D. Hunter, et, al	Journal of Bone and Mineral Research. 2000.
38	LL838- LL839	"The effect of calcium citrate on bone density in the early and mid- postmenopausal period: a randomized placebo controlled study." L.A. Ruml, et, al.	American J Theory. 1999.

39		calcium administered alone or in fixed combination with	Arzneimit tel- Forschung / Drug Research. 2001
40	LL841- LL842.	"Parathyroid hormone: an anabolic treatment for osteoporosis." P. Morley, et, al.	Current Pharm Des. 2001.
41	LL843- LL844	"Bone mineral density is inversely related to parathyroid hormone in adolescent girls." D. Bonofigli, et, al.	Horm Metab Research. 2001

42	LL845-		Internatio
	LL846	hormone in healthy	nal
		1	Journal of
		relation to serum 25-	Vitamin
		hydroxyvitamin D."	Nutr
		K. Nakamura, et, al.	Research.
			2000.
		• .	
	:		
43	LL847-	"Calcium	Journal of
	LL848	supplementation	Gerontol
•.		lowers serum	1990
		parathyroid	57
		hormone levels in	
		elderly subjects." G.	
		Kochersberger, et,	
		al.	
1	1		1

44	LL849-	"Dietary calcium	The
	LL850	and vitamin D	American
		intake in elderly	Journal of
		women: effect on	Clinical
		serum parathyroid	Nutrition.
	5	hormone and	1998
		vitamin D	
		metabolites." H.K.	
		Kinyamu, et, al.	
		•	
		·	

45	LL851-	"THE EFFECT OF	no journal
	LL852	CALCIUM	given,
		SUPPLEMENTATI	1986
		ON ON BLOOD	
		PRESSURE OF	-
		HEALTHY	
		ADULT BLACK	
		MALES AND	
		WHITE MALES	
		(PARATHYROID	
		HORMONE,	
		URINE	
		BIOCHEMICALS).	
		" Roseann Marisa	
		Lyle. 1986.	
	e.		
			· · · ·
	2 -		

46	LL853-	"Acute changes in	Clinical
	LL854	serum calcium and	Rheumato
	-	parathyroid	logy 1997.
		hormone circulation	
		levels induced by	
	-	the oral intake of	
		five currently	
		available calcium	
	-	salts in healthy male	
		volunteers." R.	
		Deroisy, et, al.	
			r.
		- -	
	2		

47	LL855	"The effect of an oral calcium load on plasma ionized calcium and parathyroid hormone concentrations in osteoporotic postmenopausal women." M. Horowitz, et, al.	Nordin. Calcif. Tissue Int. 1987.
48	LL856- LL857	"Dietary calcium and vitamin D intake in elderly	The American journal of
		women: effect on serum parathyroid hormone and vitamin D metabolites." H.K. Kinyamu, et, al.	Clinical Nutrition. 1998.

49	LL864.	1. "A CONTROLLED TRIAL OF THE EFFECT OF CALCIUM SUPPLEMENTATI ON ON BONE DENSITY IN POSTMENOPAUS AL WOMEN." Bess Dawson Huges, M.D et, al.	The New England Journal of Medicine. 1990
50	LL865- LL867	"Bioavailability and Clinical Uses of Calcium Salts." Charles Y.C. Pak, M.D. 1988.	CRN Quarterly, 1988
51	LL868	M.D. 1988. "Re: Dr. Lane in Osaka." PretiumGrp. Email. 1999.	

	LL870	"CALCIUM + VITAMIN D SHOWN EFFECTIVE IN PREVENTING HIP FRACTURES IN THE ELDERLY (70+ YEARS)." Advertisement.	
53	LL871.	Letter to Monica Reinagel. Oakford Bain. 2001.	

54	LL872-	"Acute changes in	Clinical
	LL873	serum calcium and	Rheumato
		parathyroid	logy.
		hormone circulating	
		levels induced by	
		the oral intake of	
		five currently	
		available calcium	
		salts in healthy male	
		volunteers." R.	
		Deroisy, M., et, al.	

	875	"Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women." B.L. Riggs et al.	see Row 112.
56	LL 876	"The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation." E.S. Orwoll.	Ann Intern Med, 1990.

57]	1	"Calcium supplementation and bone loss: a review of controlled clinical trials." B. Dawson-Hughes.	Am. J. Clin. Nutr., 1991
58		"Calcium supplementation reduces bone less in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age." P.J. Elders <i>et al</i> .	1991
59	LL879	"A prospective trial of the effect of vit. D supplementation on metacarpal bone loss in elderly women." B.E. Baker.	Am J Clin Nutr, 1985.

Γ		TT 000	"Bone loss in	Br J
6	50	LL880	rheumatoid arthritis	
			and primary	1, 1986.
			generalized	
			osteoarthrosis:	
			effects of	
			corticosteroids,	
			suppressive	
			antirheumatic drugs	
			and calcium	
			supplements." D.M.	
			Reid et al.	
L			· · ·	
1				
				:
		e.		
	61	LL881	"Does calcium	N Engl J
ļ			supplementation	Med,
			prevent	1987
			postmenopausal	
			bone loss? A	
			double-blind,	
			controlled clinical	
			study." B. Riis et	
			al.	
		1	1	1

62	LL882	"Calcium supplementation and bone loss in middle-aged women." E.L. Smith <i>et al.</i>	Am J Clin Nutr, 1989.
63	LL883	"Calcium supplementation and postmenopausal boneloss." L. Nilas <i>et al.</i>	Br Med J (Clin Red Ed), 1984.

64	LL884-	"Calcium and	Annals of
	LL885	vitamin D-3	Internal
	- - -	supplementation	Medicine,
	1	prevents bone loss	1996
, ·		in the spine	
		secondary to low-	
		dose corticosteroids	
		in patients with rheumatoid arthritis:	
		A randomized	
		double-blind,	
		placebo-controlled	
		study." L.M.	
		Buckley et al.	
	4 - 4		
		· · · · · · · · · · · · · · · · · · ·	
	. 9		
65	LL886	"Calcium	J
0.5		supplementation	Gerontol,
		lowers serum	1990.
			1550.
		parathyroid hormone levels in	
		elderly subjects." G	
		Kochersberger et	
		al.	
			· .
			1

66	LL887		Miner Electrolyt e Metab, 1995.
67	LL888	"Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women." B.L. Riggs	
68	LL889	"Calcium supplementation and parathyroid hormone." S. Ohgitani.	Journal of Bone and Mineral Metabolis m, 1998.

69	LL890	"Acute effects of	Am. J.
		oral phosphate-salt	Clin.
		ingestion on serum	Nutr.,
		phosphorus, serum	1988.
		ionized calcium,	
		and parathryoid	
		hormone in young	
		adults." M. Calvo	
		and H. Heath.	
	· .		
	1		
×			
	i.	3	
70	LL890	"The effect of an	Calcif.
, 0		oral calcium load or	Tissue
		plasma ionized	Int., 1987.
		calciuym and	III., 1907.
		parathyroid	
		hormone	
			-
		concentrations in	
		osteoporotic	
1		postmenopausal	
		women." M.	
		Horowitz.	
		·	
		1	
1			1

71	LL891	"The effect of	No
			journal
	-	supplementation on	listed;
		blood pressure of	Citations
		healthy adult black	from
		males and white	Dissertati
		males (parathyroid	on
		hormone, urine	Abstracts:
		biochemicals)."	DIS,
		Roseann Lyle.	1986.
	4		
			÷
72	LL891-2	"Parathyroid	British
		hormone and	Journal of
		dietary calcium."	Nutrition,
		B.J. Boucher.	2001.
<i>2</i> 1			
1			
73	LL892	"Influence of daily	Gynecolo
73	LL892	calcium and vitamir	gical
73	LL892	calcium and vitamir D supplementation	i gical Endocrino
73	LL892	calcium and vitamir D supplementation on parathyroid	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid	gical Endocrino logy,
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73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,
73	LL892	calcium and vitamir D supplementation on parathyroid hormone secretion.	gical Endocrino logy,

74	LL893	"Effects of calcium carbonate and hydroxyapatite on zinc and iron retention in postmenopausal women." B. Dawson-Hughes.	Am J Clin Nutr., 1986
75	LL894	"EFFECTS OF CALCIUM AND VITAMIN D SUPPLEMENT ON PARATHYROID FUNCTION AND FEMORAL BONE DENSITY IN ELDERLY WOMEN." P.J. Meunier, et al.	Nutritiona l Aspects of Osteoporo sis, 1991.

76	LL894	PARATHYROID GLAND AND HYPERTENSION." P.K. Pang, et al	Hypertens ion, 1991.
77	LL895	"Overnight suppression of parathyroid hormone and bone resporption markers by active absorbable algae calcium. A double-blind crossover study." T. Fujita et al.	Calcified Tissue Internatio nal, 1997.

	F		
78		"Altered diurnal	The
		regulation of blood	American
		ionized calcium and	
		serum parathyroid	clinical
		hormone	nutrition,
		concentrations	2002.
		during parenteral	
		nutrition." W. G.	
		Goodman et al.	
	:		
	110067		The
79	LL896-7	"Dietary calcium	American
		and vitamin D	1 1
		intake in elderly	journal of
		women: effect on	clinical
		serum parathyroid	nutrition,
		hormone and	1998.
		vitamin D	
		matebolites." H.K.	
1		Kinyamu.	
		· · · · · · · · · · · · · · · · · · ·	
			1
L		1	

80	LL897-8	"Correction of	Journal of
		acidosis in	the
		hemodialysis	American
		patients. Effects on	Society of
		parathyroid	Nephrolog
		hormone, calcium,	y, 1998.
		and phosphate: A	
	:	prospective study."	
		E. Movilli, et al.	
	-		
			-
		-	

81	LL898	"Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of fice currently	Clinical Rheumato logy, 1997.
		available calcium salts in healthy male volunteers." R. Deroisy.	
82	LL899	"Influence of daily calcium and vitamin D supplementation on parathyroid hormone secretion." J. Reginster et al.	Endocrino logy,

83	LL900-1	"Long-term effects	Journal of
		of calcium	Bone
		supplementation on	Mineral
		serum parathyroid	Research.
		hormone level, bone	1998.
		turnover, and bone	
		loss in elderly	
		women." B.L. Riggs	
	1		

		·	
84]	ע מ כ נ נ נ נ נ נ נ נ נ נ נ נ נ נ נ נ נ נ	Acute biochemical variations induced by calcium citrate and calcium carbonate in Type 2 liabetic patients. impaired calcium absorption in Type 2 diabetic patients with prolonged gastric emptying time." Y. Song et al.	Complicat ions, 2001.
85	L902-3	"Why oral calcium supplements may reduce renal stone disease: report of a chemical pilot study." C.P. Williams et al.	J Clin Pathol, 2001.

86	LL903-4	"Long-term	Magnes
00		0	Res, 2000.
			103, 2000.
		magnesium	
		supplementation is	
		deleterious whereas	:
		suboptimal supply	
		is beneficial for	· .
		bones in rats." J.L.	1
		Riond et al.	
			:
		۶.	
	· .		
87	LL905	"Bioavailability and	FASEB
		cost effectiveness of	
		calcium	2001.
		supplementation."	
		Cecilia A. Hale et	
		al.	
1			1 1
1		ai.	
		aı.	
		aı.	
		al.	
		aı. "	
		aı.	
88	LL905-6	-1	FASEB
88	LL905-6	"Calcium	
88	LL905-6	"Calcium bioavailability and	Journal,
88	LL905-6	"Calcium bioavailability and absroption." Ming-	
88	LL905-6	"Calcium bioavailability and	Journal,
88	LL905-6	"Calcium bioavailability and absroption." Ming-	Journal,
88	LL905-6	"Calcium bioavailability and absroption." Ming-	Journal,

89	LL908	"Parathyroid	Journal of
		hormone added to	Bone and
		established	Mineral
		hormone therapy:	Research,
	-	Effects on vertebral	2001.
	:	fracture and	
	-	maintenance of	
		bone mass after	
		parathyroid	
		hormone	
		withdrawal." F.	
		Cosman et al.	
		Cosman or an	
			1.
			1 1
90	LL908-9	"Effect of	New
		parathyroid	England
		hormone (1-34) on	Journal of
		fractures and bone	Medicine,
		mineral density in	2001.
		postmenopausal	
		women with	
		osteorporosis."	
		Bruce H. Mitlak et	
		al.	
		a1.	
	1		
		·	
	ł	1	
		1	

91LL912-4"Absorption of Calcium as the Carbonate and Citrate Salts, with Some Observations on Method." R.P. Heaney et al.Osteoporo sis Int, 1999.92LL915"Calcium in the prevention and treatment of osteoporosis." R.P. Heaney.J Intern Med, 1992.93LL916"Superior calcium absorption from calcium citrate than calcium carbonate using external forearm counting." J.A. Harvey et al.J Am Coll Nutr, 1990.				
93LL916"Superior calcium absorption from calcium carbonate using external forearm counting."Med, 1992.93LL916"Superior calcium absorption from calcium carbonate using external forearm counting."J Am Coll Nutr, 1990.	91	LL912-4	Calcium as the Carbonate and Citrate Salts, with Some Observations on Method." R.P.	sis Int,
prevention and treatment of osteoporosis." R.P. Heaney.Med, 1992.93LL916"Superior calcium absorption from calcium citrate than calcium carbonate using external forearm counting."J Am Coll Nutr, 1990.				
absorption from Nutr, calcium citrate than calcium carbonate using external forearm counting."	92	LL915	prevention and treatment of osteoporosis." R.P.	Med, 1992.
	93	LL916	absorption from calcium citrate than calcium carbonate using external forearm counting."	Nutr,

94	LL917-21	"Vitamin D,	Am J Clin
			Nutr,
		calcium gluconate	1982.
		in treatment of	
		cortical bone	
		thinning in	
		postmenopausal	
	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	women with	
		primary biliary	
		cirrhosis." Owen	
		Epstien et al.	
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95	LL922	"CALCIMATE	GNC Live
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		PLUS 800 FACT	Well Web
		SHEET."	page.
			P-B-
0.	T T 000 4	UD:11_1.11141	EASED
96	LL923-4	"Bioavailability and	
		cost effectiveness of	2001.
		calcium	2001.
		supplementation."	
		Cecilia A. Hale, et	
		al.	
	1		
	1		

97	LL925	"Calcium supplementation lowers serum parathyroid hormone levels in elderly subjects." G. Kochersberger.	See row 65.	
98	LL926-7	"The effect of	Osteoporo	-
		calcium supplementation and Tanner stage on bone density, content, and area in teenage women." T Lloyd et al.	sis Int, 1996.	

99	LL928-9	"Prevention of hip fractures by correcting calcium and vitamin D insufficiencies in elderly people." P. Meunier.	Scand J Rheumato I Suppl, 1996.
100	LL930	"Calcium absorption from calcium and a new form of calcium (CCM) in healthy male and female adolescents." J.Z. Miller et al.	Am J Clin Nutr, 1998.

101	LL931	"Bioavailability of	Am J Clin
		calcium	Nutr,
	1	supplements and the	
	:	effect of Vitamin D:	
		Comparison	
		between milk,	
		calcium carbonate,	
		and calcium	
		carbonate plus	
	:	vitamin D." L.	
		Mortensen and P.	
		Charles.	· · · ·
1			1

102	LL932-	"Prevention of	Published
	937	Osteopenia in	in Royal
		Corticosteroid-	Scoiety of
		treated Rheumatoid	Medicine
		Patients with	Internatio
		Microcrystalline	nal
		Calcium	Congress
		Hydroxyapatite	and
		Compound A	Symposiu
		Controlled Study."	m Series
	1	K.H. Nilsen	by
			Academic
			Press Inc.
			and the
			Royal
			Society of
			Medicine,
			1983
			1
			:

103	LL938	"Combined	Nutr Rev
105	22/00	calcium and	1998
	1.	vitamin D	May; 56
		Supplementation	(5 Pt 1):
		reduces bone loss	148-50.
-		and fracture	
		incidence in older	
		men and women."	
		KO O'Brien.	
		· · · ·	
		· · · · · · · · · · · · · · · · · · ·	
104	T T 020	"Clinical trial of	Curr Med
104	LL939		Curr Mea Res
		MCHC in the	1
		prevention of	<i>Opin.,</i> 1984.
		osteoporosis due to corticosteroid	1704.
		therapy." A Pines,	
		et al.	
		<i>cı ш</i> .	
		е	а. — — — — — — — — — — — — — — — — — — —

105	LL940	"Calcium absorption and achlorhydria." RR Recker.	N Engl J Med 1985 Jul 11, 313 (2) 70- 3
106	LL941- LL945	"Acute Biochemical Variations Induced by Four Different Calcium Salts in Healthy Male Volunteers." J.Y. Reginster <i>et</i> <i>al.</i>	

			· · · · · · · · ·
107	LL946- LL947	"Influence of daily calcium and vitamin D supplementation on parathyroid hormone secretion." J.Y. Reginster <i>et al.</i>	Gynecol Endocrin o, 2001.
108	LL948	"The inhibitory effect of dietary calcium on iron bioavailability: a	Nurt. Rev ., 1995
		cause for concern?" SJ Whiting.	

109	LL949	"Safety of some calcium supplements questioned." SJ Whiting.	Nutr. Rev ., 1994
110	LL950	"The acute biochemical effects of four proprietary calcium preparations." IR Reid <i>et al.</i>	Aust. N. Z. J. Med ., 1986.

111	LL951	"Long-term	American
		effects of calcium	Journal
		supplementation	of
		on bone loss &	Medicine,
		fractures in	. 1995.
		postmenopausal	
		women: a	
	:	randomized	
		controlled trial."	
		IR Reid et al.	

112	LL952-	"Long-term	Journal
	LL953	effects of calcium	of Bone
		supplementation	and
	:	on serum	Mineral
		parathyroid	Research
		hormone level,	1998.
		bone turnover,	
		and bone loss in	
		elderly women."	
		B.L. Riggs et al.	
			· · ·
			A
-			-
113	LL954	"Meta-analysis of	
· .		calcium	Ther.,
		bioavailability: a	1999.
		comparison of	
		calcium citrate	
		with calcium	
		carbonate." K	-
		Sakhaee et al.	
			`
			4
			1

114	LL955	"Gastrointestinal absorption of calcium from milk and calcium salts." MS Sheikh <i>et al.</i>	of
115	LL956	"Calcium absorption from a new calcium delivery system (CCM)." KT Smith <i>et al.</i>	Calcif Tissue Internatio nal, 1987.

·			
116	LL957- LL962	"Microcrystalline hydroxyapatite compound in prevention of Bone loss in corticosteroid- treated patients with chronic active hepatitis." A. Stellon <i>et al.</i>	Postgrad uate Medicine Journal , 1985.
117	LL963	"The inhibitory effect of dietary calcium on iron bioavailability: a cause for concern?" SJ Whiting.	Nutr Rev., 1995.

119LL965- LL969"THE EFFECT OF WHOLE- BONE EXTRACT ON 47Ca ABSORPTION IN THE ELDERLY." A.C.M. Windsor et al.Age and Age ing , 1973.	118	LL964	"Safety of some calcium supplements questioned." SH Whiting.	Nutr Rev., 1994.
	119		OF WHOLE- BONE EXTRACT ON ⁴⁷ Ca ABSORPTION IN THE ELDERLY." A.C.M. Windsor	Ageing,

ł

120	LL970- LL971	"Correcting calcium nutritional deficiency prevents spine fractures in elderly women." RR Recher <i>et al</i> .	Journal of Bone Mineral Research , 1996.
121	LL971-	"Vitamin D3 and	The New
	LL972	calcium to prevent hip fractures in the elderly women." MC Chapuy <i>et al.</i>	E 1

122 LL973-	- "Superior	Journal
LL975	Calcium	of the
	Absorption from	American
	Calcium Citrate	College
	than Clacium	of
	Carbonate Using	Nutrition,
	External Forearm	1990.
	Counting." Jean	
	A. Harvey et al.	
	1	

123	LL976- LL977	"CALCIUM BIOAVAILABILI TY FROM CALCIUM CARBONATE AND CALCIUM CITRATE." Michael J. Nicar and Charles Pak.	Journal of Clinical Endocrin ology and Metabolis m, 1985.
124	LL978	"Calcium supplementation lowers serum parathyroid hormone levels in elderly subjects." G Kochersberger <i>et al.</i>	Journal of Gerontol , 1990.

	LL979- LL980	"The effect of calcium supplementation and Tanner stage on bone density, content and area in teenage women." T Lloyd <i>et al.</i>	Osteopor osis Internatio nal , 1996.
126	LL981- LL982	"Prevention of hip fractures by correcting calcium and vitamin D insufficiencies in elderly people." P.	Rheumato l Suppl , 1996.
		Meunier.	

127	LL983	"Calcium	American
		absorption from	Journal
		calcium carbonate	of
		and a new form of	Clinical
		calcium (CCM) in	Nutrition,
ĥ		healthy male and	1988.
		female	
		adolescents." JZ	
		Miller et al.	
			· .
		· · · · ·	
	1		

128	LL984	"Bioavailability	American			
		of calcium	Journal			
		supplements and	of			
		the effect of	Clinical			•
		Vitamin D:	Nutrition,			
		comparisons	1996.			
		between mild,				
		calcium				
		carbonate, and				
		calcium carbonate				
		plus vitamin D."				
		L Mortensen and P Charles.	;			
		P Charles.				
			·			
				- -		

129	LL985-	"Prevention of	Royal
	LL990	Osteopenia in	Society of
		Corticosteroid-	Medicine
		treated	Internatio
		Rheumatoid	nal
		Patients with	Congress
		Microcrystalline	and
		Calcium	Symposiu
		Hydroxyapatite	m Series ,
		Compound – A	1983.
		Controlled	
		Study." K.H.	
		Nilsen et al.	
	-		
L			

130	LL991	"Combined	See
		calcium and	<i>Row103</i> .
		vitamin D	
		Supplementation	
		reduces bone loss	
		and fracture	
		incidence in older	
		men and women."	
		KO O'Brien.	

131	LL992	"Clinical trial of microcrystalline hydroxyapatite compound ('Ossopan') in the prevention of osteoporosis due to corticosteroid therapy." A Pines <i>et al</i> .	See Row 104.
132	LL993	"Calcium absorption and achlorhydria." RR Recker. <i>The New</i> <i>England Journal</i> <i>of Medicine</i> . 1985.	See Row 105.

133	LL994-	"Acute	See Row
	LL998	Biochemical	106.
		Variations	
		Induced by Four	
	:	Different Calcium	
		Salts in Healthy	
		Male Volunteers."	
		J.Y. Reginster, D.	
		Denis, V. Bartsch,	
		R. Deroisy, B.	
		Zegels, and P.	
		Franchimont.	
		Osteoporosis	
		International .	
		1993.	

124	T T 000	ыт ст с	0
134	LL999-	"Influence of	See Row
	LL1000	daily calcium and	107.
		vitamin D	
		supplementation	
		on parathyroid	
		hormone	
		secretion." J.Y.	
		Reginster, B.	
		Zegels, E.	
		Legeune, M.C.	
		Micheletti, A.N.	
		Taquet, and A.	
		Albert. Gynecol	
	· .	Endocrinol. 2001.	
			-
	1		
	·		

135	LL1001	"The acute	See Row
		biochemical	110.
		effects of four	
	44 	proprietary	
		calcium	
		preparations." IR	
		Reid, BA	
		Schooler, SF	
		Hannan, and HK	
		Ibbertson. Aust N Z J Med. 1986.	
		Z J Mea . 1980.	

136	LL1002	"Long-term	See Row
		effects of calcium	111.
		supplementation	
		on bone loss and	
		fractures in	
		postmenopausal	
		women: a	
	r.	randomized	
		controlled trial."	
		IR Reid, RW	
		Ames, MC Evans,	
		GD Gamble, and	
		SJ Sharpe.	
		American Journal	
		of Medicine .	
	:	1995.	
	:		
	· · ·		
	:		
		· · ·	

137	LL1003-	"Long-term	See Row
	LL1004	effects of calcium	112.
		supplementation	
		on serum	
		parathyroid	
		hormone level,	
		bone turnover,	
		and bone loss in	
		elderly women."	
		B.L. Riggs, W.M.	
		O'Fallon, J.	
		Muhs, M.K.	
		O'Connor, R.	
		Kumar, and LJ	
		Melton 3 rd .	
		Journal of Bone	
		and Mineral	
		Research . 1998.	
		· · · · ·	

138	LL1005	"Meta-analysis of	See Row
		calcium	113.
		bioavailability: a	
		comparison of	
-		calcium citrate	-
		with calcium	
		carbonate." K	
	4 2	Sakhaee, T	
	-	Bhuket, B Adams-	
		Huet, and DS	
		Rao. American J	
		Ther. 1999.	
	3	:	
		а.	
		-	
		-	:
	l		

139	LL1006	"Gastrointestinal	See Row
		absorption of	114.
		calcium from milk	
		and calcium	
		salts." MS Sheikh,	
		CA Santa Ana,	
		MJ Nicar, LR	
		Schiller, and JS	
		Fordtran. The	
		New England	
		Journal of	
		Medicine . 1987.	

140	LL1007	"Calcium absorption from a new calcium delivery system (CCM)." KT Smith, RP Heaney, L Flora, and SM Hinders. <i>Calcif Tissue</i> <i>International</i> . 1987.	See Row 115.

141	LL1008-	"THE EFFECT	See Row
	LL1012	OF WHOLE-	119.
		BONE	
	- - -	EXTRACT ON	
		⁴⁷ Ca	
		ABSORPTION	
		IN THE	
		ELDERLY."	
		A.C.M. Windsor,	
		D.P. Misra, J.M.	· · ·
		Loudon, and G.E.	
	1	Staddon. Age and	
		Ageing . 1973.	
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	LL1013- LL1018	"Microcrystalline hydroxyapatite compound in prevention of Bone loss in corticosteroid- treated patients with chronic active hepatitis."	See Row 116.
		A. Stellon <i>et al</i> .	
143	LL1019	Illegible copy of 2"x2" text box.	N/a

144	LL1020-	"Dose	Journal
	LL1026	Dependency of	of Bone
		Calcium	and
		Absorption: A	Mineral
		Comparison of	Research,
		Calcium	1988
		Carbonate and	
		Calcium Citrate."	1
		Jean A. Harvey <i>et</i>	
		al.	
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145	LL1027-	USPTO Information	n/a
	1050		

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146	LL1051	"Calcium	J Bone
1		Bioavailability from	Miner
		Heated Oyster Shell-	Metab.
		Seaweed Calcium	1996.
		(Active Absorbable	1990.
		•	
		Algae Calcium) as	
	-	Assessed by	1
		Urinary Calcium	
		Excretion." T.	
		Fujita, et al.	
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147	LT 1051-2	"Calcium Paradox	I Bone
147	LL1051-2	"Calcium Paradox	J Bone Minor
147	LL1051-2	Disease: Calcium	Miner
147	LL1051-2	Disease: Calcium Deficiency	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting	Miner
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload."	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload."	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
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147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
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147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,
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147	LL1051-2	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G.	Miner Metab,

148	LL1052	"Calcium Supplement and Parathyroid Hormone." S. Ohgitani, et al.	J Bone Miner Metab., 1998.
149	LL1052-3	"Degenerative Joint Disease: An Example of Calcium Paradox." T. Fujita.	J Bone Miner Metab., 1998.
150	LL1053	"Heated Oyster Shell with Algae Ingredient (AAACa) Decreases Urinary Oxalate Excretion." S. Ohgitani and T. Fujita.	no journal given; study conducted at Calcium Research Instit. In Japan.

151	LL1053-4	"Increase of Intestinal Calcium Absorption and Bone Mineral Density by Heated Algal-Ingredient (HAI) in Rats." T. Fujita, et al.	no journal given; study conducted at Institute of Science and Technolog y in Japan.
152	LL1054	"Calcium Paradox	n/a
132	1004	Disease: Calcium Deficiency Prompting Secondary Hyperparathyroidis m and Cellular Calcium Overload." T. Fujita and G. Palmieri.	11 <i>1</i> a

153	LL1054	"Peripheral	J Bone
		Computed	Miner
		Tomography	Metab.,
		(PQCT) Detected	2000.
		Short Term Effect	
		of Heated Oyster	· ·
		Shell Without	
		(AACa) and With	
		Heated Algal	
	· · · · ·	Ingredient (HAI)	
		(AAACa) A Double	
		Blind Comparison	:
		with Caco(3) and	
		Placebo." T. Fujita,	
		et al.	
			-
154	LL1055	"Effect of Calcium	Miner
	•	Supplementation on	
		Bone Density and	e Metab.,
		Parathyroid	1995.
		Function in Elderly	
		Subjects." T. Fujita,	
		et al.	
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155	LL1055-6	"A Three-Year	J Bone
		Comparative Trial	Miner
		in Osteoporosis	Metab.,
		Treatment: Effect of	1997.
1		Combined	
4 A A		Alfacalcidol and	
5		Elcatonin." T.	
		Fujita, et al.	
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		i.	
156	LL1056	"Effects of Amino	J Bone
		Acid Calcium: Its	Miner
		Bioavailability on	Met.,
		Intestinal	1998.
		Absorption,	
		Osteoporosis and	
		Removal of	
		Plutonium in	
		Animals." S.	
		Fukuda.	
		Fukuda.	
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157	LL1056	"Overnight	Calcif
		Suppression of	Tissue
		Parathyroid	Int., 1997.
		Hormone and Bone	
		Resorption Markers	
		By Active	
		Absorbable Algae	
		Calcium. A Double-	
		Blind Crossover	
		Study." T. Fujita, et	
		al.	
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158	LL1057-	USPTO Patent Full-	n/a
200	1068	Text and Image	
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25 October 1999

Andrew J. Lane President LaneLabs 110 Commerce Drive Allendale, New Jersey 07401

Dear Mr. Lane:

You asked that I provide you with an evaluation of the AAACa product and its associated research. You also asked several questions in your cover letter. Here is my best attempt to provide you with the answers you requested. I have tried to be as restrained in my approach as I could, in order not to run your bill up unduly. So, please let me know if I can help further.

In addition to responding specifically to your questions and to the materials supplied, I have taken the liberty of preparing a brief background treatment of some of the issues dealing with bone remodeling and with the effects of calcium supplementation thereon. I believe you will need this in order to have the context in which claims about "building bone" can be understood or make sense or be defended.

In my treatment I have confined myself pretty much to the biological science. I am certain you recognize that successful marketing of a product is based on something more than the involved science. Acquiring rights to the product is a business decision, and whether you should do that or not is not within my arena of competence to advise.

You raised two points in your letter that I think I can deal best with here, before launching into a more detailed review of the Fujix material.

- The fact that these studies were done in Japanese individuals would not, in my opinion, constitute a barrier to their acceptance by the scientific community or to their generalizability to other races.
- What would be a barrier to general scientific acceptance is the fact that the studies have all been performed by an individual who has a commercial interest in the product. This is not, for a moment, to suggest dishonesty, just the absence of full scientific objectivity.

Page 1

Exhibit 3 WYL4:6 9007 7 9n8 Andrew J. Lane 25 October 1999 Page 2

• You mention that the elderly showed an increase in BMD, and characterized them as a "tough" population in which to show such a change. Actually the opposite is the case. They are the easiest group in which to show that kind of change. This is partly because of the phenomenon known as the remodeling transient, which I describe in greater detail in the attachment, and partly because the calcium requirement actually rises in the elderly, so that the intake of an elderly person tends to be more deficient than that of younger individuals, and hence the response to supplementation is relatively greater.

Sincerely yours,

Robert P. Heaney, M.D. Enclosures 1<u>1</u>1003

BONE "BUILDING" AND THE REMODELING TRANSIENT

Bone Remodeling

Bone is continuously remodeling itself, and the effects of calcium (and pharmacotherapy) on the remodeling process produce changes in BMD that need to be distinguished from changes in steady state bone balance.

In the remodeling process, microscopic units of bone are actually eaten away (the process known as "bone resorption"), and then later replaced with fresh new bone, (the process known as "bone formation"). The balance between the two processes is what determines whether we are gaining bone, losing bone, or maintaining bone. Incidentally, all bone loss and gain come about in this way. Bone mass changes only through shifts in remodeling balance.

Remodeling removes damaged portions of the structure and helps keep our bones resilient. A principal determinant of the total quantity of bone remodeling in the skeleton as a whole is the amount of parathyroid hormone (PTH) being produced and circulating in the blood. PTH secretion, in turn, is inversely proportional to effective calcium intake. The site of action of PTH is both at the initiation of the remodeling process, and on the resorption step. PTH is often thought of as a bone weakening hormone, because it does stimulate bone breakdown. When calcium intake is not adequate to offset daily losses, it is PTH that causes the remodeling imbalance that leads to bone loss (thereby making calcium available for other body needs). But whether bone mass is reduced or not is a function of the calcium intake. At high calcium intakes, PTH actually leads to an increase in bone in certain skeletal regions.

At the remodeling site the processes of resorption and formation are always asynchronous, i.e., the demolition and repair processes cannot go on simultaneously. Rather, as with remodeling of a building, the demolition precedes the repair. While this is inevitably true locally, when averaged over the skeleton as a whole, there should be about as much repair as demolition occurring on any given day. When, in the steady state, there is an excess of demolition, then more bone is being broken down than is being replaced and bone mass is decreasing. Conversely, as during growth, when formation exceeds resorption, bone is being "built", Both of these statements apply to the steady state situation, and it is to this steady state that we would normally apply the term "bone building". This emphasis is important because, when remodeling is altered, it takes some time before a new steady state is reached. The time required, at a local site, to complete the remodeling process, from beginning of destruction to the conclusion of repair, is typically on the order of 3-6 months in healthy young adults, and six months to two years in older individuals.

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Exhibit 3 ₩∀/₽:6 9002 '₽ ⁹n∀ Perhaps a helpful way to think about the consequences of this asynchrony is to compare our skeletons to a large hotel. Let's say that you have 500 rooms. After the hotel has been in use for some time, there will be rooms that will have to be taken out of service because they need repair. Also, at the same time you, as manager, must deal with decisions about whether to expand by adding on another wing, or to constrict, by converting space to some other use. Repair is analogous to remodeling of the skeleton, and expansion and conversion are analogous to bone building and bone loss, respectively.

Now, if your clientele is typically dominated by rock groups and their followers, you will constantly be sustaining a lot of damage that will require a lot of repair. Thus, on any given night perhaps 50 of your rooms will be unavailable for rent, i.e., you can only use 450 rooms, because 50 are being repainted, recarpeted, or their plumbing repaired. Assume that you, as manager, make a decision to change your clientele, and not to accept reservations from these destructive groups, and to focus instead on marketing to temperance groups and conventions of church women. In the weeks and months following this policy decision, you will experience some of the old rooms coming back into service as you complete their repairs, but you will be taking a lot fewer rooms out of service. Thus, instead of 450 rooms available on a given night under the old reservations policy, you will experience an increase to 460, 470, 480, etc., until you reach some minimum level of repair below which you can never drop. Have you "built" more hotel? Well, you certainly have more rooms to rent than you did a few weeks ago, and you generate more revenue. So in one sense you have more hotel, but in another sense what you have is simply more usable hotel.

Precisely the same is true of the skeleton. Having more usable skeleton is just as good for skeletal strength as having more rooms to rent is good for your hotel business. But it is not the same thing as building more bone or more hotel, in the strict sense of the term.

The Bone Remodeling Transient

In the hotel business the critical factor is the change in clientele, while in the skeleton the critical factor is the change in the level of PTH. The elderly typically have both less bone and substantially elevated PTH levels. Thus they have fewer "rooms" to start with and more rooms out of service because of high remodeling. In certain skeletal regions, that can mean that as much as 10–20 percent of the skeleton is currently being remodeled, and is not, therefore, structurally useful now. Why is remodeling rate so high? One major reason is effective calcium deficiency – or perhaps more precisely – decreased ability with advancing age to adapt to an insufficient intake. Any factor that reduces that remodeling rate (such as supplemental calcium) will give you an immediate gain in usable skeleton. The phenomenon is called a "remodeling transient". The reason why it is called "transient" will be evident in what follows.

Page 4

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Exhibit 3 WA84:6 2006 4.48 Incidentally, this transient is the basis for my statement in the cover letter to the effect that an increase in BMD following calcium is easier to see in the elderly than at any other time of life. The elderly are simply remodeling more of their skeleton, and that remodeling is suppressible when one gives extra calcium. These responses are a part of the reason why science now believes the elderly are often calcium deficient.

But a problem remains as to how one interprets the data from clinical studies in which bone mass is measured before starting calcium supplementation, and then again after some period of treatment. I am enclosing a figure adapted from a chapter I wrote on this topic, which shows schematically the time course of bone mineral density under conditions of no calcium supplementation and then with supplementation in two hypothetical groups of patients. You will notice from the figure that there is an immediate rise in the treated group, lasting about a year, following which there is a leveling off of bone mineral density and then a gradual decline with time. The rise is the transient. You will notice also that, in the untreated group, there is a steady decline with time. Further, you will notice, in this hypothetical case, that the rates of decline in the two groups after the remodeling transient is over are different, with the calcium-supplemented individuals losing at a slower rate than the unsupplemented. Finally, you will notice that if you make only two measurements, one before and the other after some period of treatment, what appears to happen will be different depending upon the time of your second measurement. With a short interval, there is a very substantial increase in measurable bone (i.e., BMD), but as the interval stretches out, the supplementation appears to be less and less effective. But those different appearances are simply an artifact of when we choose to measure. Clearly the calcium supplementation is having a positive effect throughout. The calciumsupplemented individual, at all time points, has more usable bone (and therefore more bone strength) than the unsupplemented individual. Moreover, after the transient, the rate of bone loss is reduced in the calciumsupplemented group. So, for both reasons, the supplemented individual enjoys a benefit of the extra calcium.

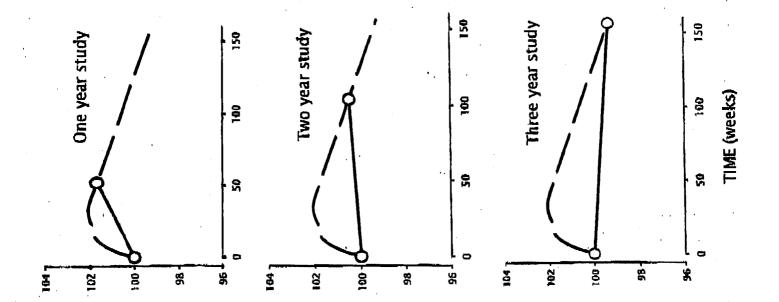
But a semantic question arises as to whether this is "building bone". To paraphrase President Clinton: What do you mean by the word "build"?

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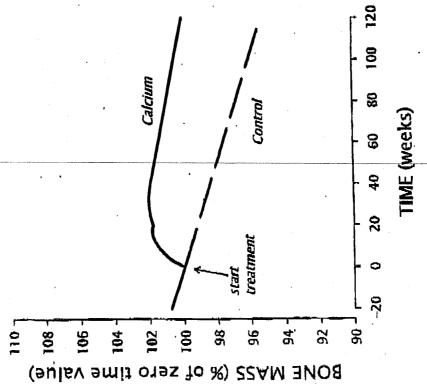


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CALCIUM, CALCIUM SALTS, and AAACa

Calcium, of course, exists in nature in combination with a variety of anions. The principal calcium supplement salts in use in the U.S. are calcium carbonate, the various calcium phosphates, and a variety of calcium salts of organic acids, such as the citrate, malate, glubionate, lactate, etc. Generally the anion makes relatively little difference, and despite wide variation in aqueous solubility (spanning 4–5 orders of magnitude!), most of the calcium salts are absorbed at very nearly the same efficiency (generally in the range of 25–35 percent at ingested loads in the range of 300 mg). Furthermore, with some relatively minor exceptions, calcium is dissociated from its anion and loses any connection with it in the process of being absorbed. Again, with some minor exceptions, the principal significance of the anion relates to issues such as tablet bulk, palatability, cost, and other such considerations.

It is true that complex salts such as calcium citrate malate are somewhat more absorbable than calcium carbonate, which in turn is more absorbable than calcium phosphate, etc. But the differences are really quite small, and the advantages associated with one or another form come more from the marketing edge they confer on their products than from a consideration of nutritional economics. (Thus, taking a couple extra Tums® a week will obliterate any advantage that CCM may have over calcium carbonate, at far less cost than getting all one's supplemental calcium from CCM.)

While many manufacturers would like to think that they have a special ingredient which somehow enhances the absorbability or the effectiveness of the calcium in their product, there is no general scientific acceptance that such special ingredients exist. That is not to say that some might not be discovered, just that none is recognized today.

Having said that, I must also note that the Fujix AAACa is chemically and pharmaceutically different from other calcium supplement formulations in that its principal sait appears to be calcium hydroxide, and it contains the so-called heated algal ingredient (HAI). To my knowledge, calcium hydroxide is not used in any other product, and its absorbability has never been directly tested using generally accepted methods. What we know about its absorbability, as well as of the effect of the HAI, comes to us solely from the work of the Fujix Company and of Dr. Fujita himself. It is conceivable that calcium hydroxide may be substantially more absorbable than the more usual salts, or that HAI enhances absorbability (particularly in individuals with gastric acid, although gastric acid is not actually necessary for calcium absorption, despite popular lore to the contrary). The papers you supplied do provide some information on both points and I shall evaluate that evidence below.

Finally, calcium absorbability differences, to the extent any exist, may have a greater marketing benefit than a nutritional benefit. This is because

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unabsorbed calcium in the food residue produces useful and important detoxification effects in the intestine in its own right. From purely nutritional considerations, one should be interested not in enhancing calcium absorbability, but in increasing calcium intake. Dr. Fujita to the contrary notwithstanding, the problem with today's diets is not that the calcium is poorly absorbable but that the calcium intake is so much lower than would have been the case under primitive conditions.

INTERVIEW WITH TAKUO FUJITA

Dr. Fujita is a senior clinical bone investigator in Japan, is well known internationally, and has contributed usefully to the advance of the field. As is the case for any human being, he has viewpoints and paradigms within which he interprets data, and these will not always be shared universally among his peers. Thus the comments that I shall offer below are not so much criticism (although in several instances I believe the statements attributed to him are factually incorrect), as they are an attempt to give LaneLabs the sense that there may be other views on some of these topics.

To begin with, absorption of calcium carbonate is not "very poor" even in the total absence of stomach acid. This is simply an error of fact. Calcium carbonate is actually slightly more absorbable than the calcium of milk, as shown in literally dozens of experiments using radioactive calcium-labeled calcium sources. And milk calcium absorbability reflects the absorbability of mixed food diet calcium generally. (Milk is, in effect, the gold standard here.) Second, to the extent that AAACa can be equated with calcium hydroxide, it is not true to say that calcium hydroxide is "highly" soluble. It is certainly more soluble than calcium carbonate (see any handbook of chemistry and physics), but when placed in water it forms a milky particulate suspension, rather than going totally into solution. When 500 mg of calcium as the hydroxide is placed into 100 mL of hot water, less than 10% will go into solution.

Similarly, it is not true that the phosphorus of milk reduces the absorbability of its calcium. Over very broad ranges of Ca:P ratio (from 0.2 to 2.0), phosphorus intake has no influence whatsoever on calcium absorption. This has been demonstrated by multiple investigators, using a variety of methods. The best explanation that I know of for the seeming paradox of what happens in the test tube and what happens in the intestine is that phosphorus is fairly readily absorbed (60-80 percent) so that residual phosphorus in food is not present in sufficient quantity to complex the calcium in the intestinal contents. (There is also the fact that no theory exists for the highly concentrated mixture that is the chyme, and extrapolations from dilute solution chemistry to this milieu can be very misleading.)

The foregoing comments on Dr. Fujita's statements about other sources of calcium are not particularly relevant to the issue of whether AAACa could be a good source of calcium, or could be a useful product for a company to market. Dr. Fujita's statements reflect, instead, the theoretical (rather than evidence-based) type of argumentation that is commonly employed to convince someone that a particular product might be better than another. But such arguments never carry any weight by themselves; they must be buttressed by facts. I believe that Dr. Fujita is substantially in error on the

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Exhibit 3 MA84:0 0005 4 -18 N A foregoing points, but I suspect it is simply a matter of uncritically thinking about some of these issues because of an understandable desire to promote his own brainchild. As I say, while AAACa could be better than some other forms, in terms of absorbability, it doesn't have to be highly absorbable to be good in its own right, and it would not detract from AAACa to say that other forms of calcium are good, too. As implied in the brief treatment enclosed on "Calcium, Calcium Sources, and AAACa", as far as the body and the bones are concerned, all calcium looks pretty much alike. As stated there, calcium loses its association with whatever may have accompanied it in the tablet as soon as it is absorbed (if not already in the chyme). Outside of the halls of the supplement manufacturers, in the general nutrition and bone biologic communities, calcium is calcium. Period. (The scientific community may be wrong. So I don't state this so much as fact, as to tell you what the prevailing view is.)

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EVALUATION OF SCIENTIFIC PAPERS AND DOCUMENTATION PROVIDED BY FUJIX

Compositional Data and Patent

As stated in the patent and inferred in several other pieces of documentation, the calcium form in AAACa is principally calcium hydroxide, though statements are made to the effect that there is some calcium oxide, as well. The popular name for calcium oxide is lime, which is caustic, and one presumes that the manufacturers would not have created an oral dosage form that contained a caustic compound. Indeed, the composition table supplied by Fujix is not compatible with the presence of any calcium oxide at all. As noted in earlier correspondence, the composition table cannot be reconciled with all of the calcium being present in the form of calcium hydroxide, either, and what the remaining calcium species may be, or whether the analysis is incorrect, is uncertain.

The current product also contains 25% citric acid by weight. When added to an aqueous medium about one-fourth of AAACa will convert to calcium citrate.

In several places, both in the patent document and in earlier papers by Dr. Fujita, AAACa is characterized as "active amino acid" calcium. However, the composition table states that the amino acid level is too low to be quantified. Furthermore, the method of calcining the oyster shell powder would be expected to destroy any organic material. The patent states that the absence of oxygen in the calcining process somehow preserves the amino acids, but no evidence is presented to support that claim, and it is hard to imagine that such amino acids, even if present, could be exerting any biological effect if they are at levels too low to be detected. Furthermore, the patent states that the amino acids are somehow "layered" between tiers of calcium oxide crystals, but again no evidence is provided to support that statement.

Finally one notes in passing how flexible and fluid the name has been over the past few years. At one time the product was called HOSS – "heated oyster shell seaweed calcium"; then it became OSE – "oyster shell electrolysate"; then AAACa – "active amino acid calcium"; then that acronym was retained but shifted to mean "active absorbable algal calcium"; and now it is just "active absorbable calcium" or "AAACa". The shift away from the term "active amino acid" in the title suggests to me that the authors have abandoned their earlier contention in this regard. Also, one must wonder whether the product itself, or just its name, has changed over these years. This is not just nit-picking. If the product has changed in important ways, much of the documentation provided with respect to earlier formulations must be judged irrelevant for the current AAACa with HAI.

Page 11

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Exhibit 3 WW67:6 9007 '7 '3nV The current process seems to include the admixture of a heated algal component (HAI). I am not experienced in reading patents, but it would seem that U.S. Patent 5,296,246,000 does not cover the HAI component of the current product. This distinction may be important because some of the documentation provided (see below) suggests that HAI may have a benefit in its own right. If so, HAI could be added to any calcium source to produce that benefit.

Finally, it may be noted that, on page 3 of the patent, under the heading "Background of the Invention" there are many serious misstatements of fact. Specifically, paragraphs four through seven are substantially or totally incorrect.

Evaluation of Published Scientific Papers

N.B.: I have focused my review mainly on the papers that have been published, rather than on the poster presentations and manuscripts provided. I have also checked References 1 to 3 of the Fukuda paper.

- JBMM 1997 This paper shows that AAACa produces a bone benefit. No comparative data are provided for other calcium sources. The production of a bone benefit is presumptive evidence that the product is absorbable.
- Min Elect Met 1995 See below.
- CTI 1996 These are the same patients as described in the foregoing publication. The method of analysis of the data employed by the authors is incorrect, statistically. Furthermore, it is hard to evaluate the data provided, inasmuch as the numbers of individuals at each sampling point decline with follow-up, and the within-individual data are not supplied. In any case, there appears to be little apparent difference between plain calcium carbonate and AAACa in this study.
- OI 1997 This paper is simply a comment. It contains no experimental data.
- CTI 1997 This paper presents a comparison of two dosing regimens of AAACa. There is no comparison with other calcium sources. Although absorption efficiency is not directly measured, the data show that the product is absorbable. The suppression of PTH and the other changes described have also been shown by other investigators for other forms of calcium.
- JBMM 1998 Fukuda This paper presents the only comparative data for AAACa and another calcium source (calcium carbonate). It is, however, performed in animals. Figures 1 and 2 show clearly higher blood levels of calcium with AAACa than with calcium carbonate in both rats and dogs, but the details of these infusion experiments are not given. Indeed, the experiments described in the Methods section seem

Page 12

not to be related to the data of these two figures at all. The sizes and physical form of the infused loads are not given, and the degree of elevation of blood calcium produced would indicate either huge loads, or major mucosal damage associated with the load. To give some idea of the magnitude of the increase, the degree of hypercalcemia produced in the rats with AAACa, if it had occurred in humans, could well be fatal. The breaking force and histomorphometric data in Figures 3 and 4 do not compare AAACa with calcium carbonate.

- Although not provided in sufficient detail for any kind of proper evaluation, the poster presentations suggest activity of the heated algal ingredient (HAI). The Abstract states that, in a four-way trial in humans, AACa without HAI was not different from calcium carbonate or placebo.
- Bone Miner 1990 This is a study of a single product (OSE presumably later called AACa), showing a small effect at one site (but not others) in elderly women. If OSE is similar to AAACa, this could be taken as evidence of absorbability, but the paper provides no comparative data.
- NRIZ 1997 As far as I can tell from the English language Abstract (the original paper is in Japanese) this is a poorly designed experiment which shows, for the most part, comparability between AAACa and milk calcium, though it does appear that the calcium loads were different for the two sources. The only point of difference between the two products was in PTH level, and this could mean greater absorbability for AAACa, but there are other interpretations just as plausible, and more information would be needed before one could be certain of the meaning of this work.
- Ref. 1 from the Fukuda paper (Bone Miner 1988 not supplied by Dr. Fujita) actually contains the only comparative human data that are interpretable with respect to AAACa and calcium carbonate. In four patients with hypocalcemia due to hypoparathyroidism, OSE Ca increased serum calcium to a greater extent than calcium carbonate; moreover, there was a much greater rise in urine calcium with OSE Ca. These data indicate that OSE Ca is absorbable, and in this case, more so than a calcium carbonate preparation (type unspecified). Given the other clinical data, I believe absorbability for OSE Ca (if it is the same as HOSS, AACa, and AAACa) can be considered to be very probable. Relative absorbability (vis-à-vis other salts) is less clear.

Comment

The product, AAACa, is a calcium source of uncertain composition, but presumably principally calcium hydroxide (and partly calcium citrate when in aqueous suspension). Calcium hydroxide is a calcium source new to human

3

Page 13

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supplementation, and its properties have not been well characterized. Calcium citrate is well studied, and by itself is no more absorbable than calcium carbonate. From the data provided, it would appear that AAACa is absorbable, but no proper absorbability tests have been performed, and no convincing comparative data have been brought forth that would support claims of superiority. The heated algal ingredient (HAI) is apparently new to the product, and fragmentary data are provided suggesting that it may exert some calcium-enhancing activity in its right. These need to be confirmed.

As noted earlier, superior absorbability is not necessarily nutritionally advantageous; however, it could confer a marketing advantage on a product. The data that have been provided to me would not constitute convincing evidence of such superiority, and if LaneLabs were to decide to utilize this product, some test establishing superior absorbability would seem to be mandatory. The best such test would not be feasible for this product, since the test would require the introduction of an isotopic tracer into the product, and given the product's physical characteristics, that would not be possible. Hence it would be necessary to use less precise methods, such as comparative hypercalcemia or hypercalciuria produced by equivalent calcium loads ingested in two or more chemical forms. Such tests are feasible and could be done for relatively modest cost. Advertising that claimed superiority without more convincing evidence than is now provided by Fujix, would invite challenge by either the FTC or the Better Business Bureau (cf. the action by SmithKline Beecham against Mission Pharmacal, with regard to the latter's unsupportable claims of superior absorbability for calcium citrate).

If LaneLabs is interested in pursuing this venture further, it may be that the company could split the cost of the comparative absorbability testing with Fujix. My own laboratory could perform the indicated tests for you, or if you wished a further degree of independence, could help you design the needed experiment and place it with another investigator.

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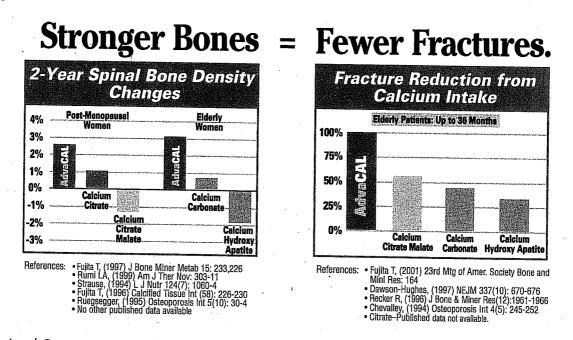
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BONE & JOINT HEALTH



"AdvaCAL" is the #1 Bone Building Calcium. Period."

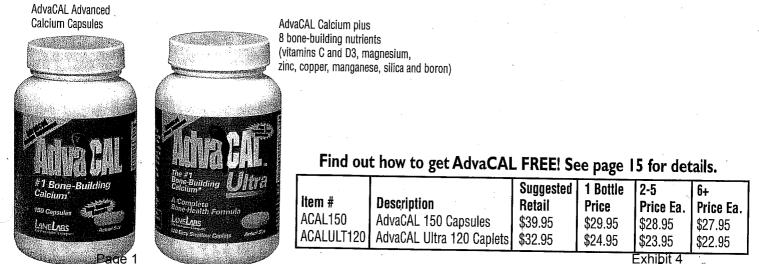
Dr. I. William Lane



"The National Osteoporosis Foundation reports that most Americans are calcium deficient. Osteoporosis has become a national epidemic. Osteoporosis is reversible if you take the right type of calcium. I recommend AdvaCAL to men and women of all ages. The pills are small, easy-to-swallow and amazingly effective. It's the only calcium I've seen that has been shown over and over to build bone density."

— Dr. I. William Lane

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Exercise and a healthy diet with adequate daily calcium intakes may help younger white and Asian women reduce their osteoporosis risk in later life. Calcium intakes above 2000 mg per day are not likely to provide extra benefit.

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease

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Heated Oyster Shell-Seaweed Calcium (AAA Ca) on Osteoporosis

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Abstract. A randomized. prospective, double-blind test was carried out to compare the effects of heated oyster shell-seaweed calcium (AAA Ca), calcium carbonate, and placebo in 58 elderly, hospitalized women with the mean age of 80 divided into three groups. Group A received 900 mg/day Ca as AAA Ca, Group B 900 mg/day Ca as CaCO₃, and Group C placebo besides regular hospital diet containing approximately 600 mg Ca/day for 24 months. From the 25th to the 30th month, all groups were given AAA Ca. Lumbar spine and radial bone mineral density (BMD) were measured at 3-month intervals. Urinary Ca/Cr and serum alkaline phosphatase, intact and midportion serum parathyroid hormone (PTH), and calcitonin were also measured at intervals. From the 6th to the 24th month of the study, the ratio of lumbar spine BMD (L2-L, by DPX, Lunar) to the hasal pretest value was consistently and significantly higher in Group A than Group C but not higher in Group B than in Group C. PTH, measured 12 months after the beginning of the study, was lower in Group A than in Group C. but no significant difference was found between Groups B and C. At 3 months after the placebo was switched to AAA Ca in Group C, serum PTH was significantly decreased from the level during placebo supplement. Morning urine Ca/Cr dccreased in Groups A after 18 months and in B after 12 months, but not in C. Serum alkaline phosphatase decreased in Group A significantly compared with Group C, but not in Group B. AAA Ca appears to be effective for increasing BMD in elderly subjects.

Key words: Heated oyster shell seaweed Ca — Osteoporosis — Parathyroid hormone — Alkaline phosphatase — Urinary Ca/Cr.

Oyster shell heated in vacuo (AA Ca) was reported to be absorbed from the intestine more efficiently than calcium carbonate [1, 2]. It also increases radial bone mineral density (BMD) (measured by single photon absorptiometry) and spinal trahecular BMD (measured by quantitative computed tomography [3, 4]). Since heated oyster shell-seaweed calcium (AAA Ca, Fujix, Tokyo) was found to be even more efficiently absorbed than oyster shell heated in vacuo in intact and parathyroidectomized rats [5], it appears worthwhile to compare the effect of this new calcium prep-

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Page 1

aration on bone density with that of widely used calcium carbonate in elderly subjects with reduced intestinal Ca absorption. A randomized, prospective, and double-blind controlled study was therefore undertaken on a group of elderly hospitalized subjects to evaluate the effect of AAA Ca on BMD and parameters of calcium metabolism in comparison with calcium carbonate and placebo.

Subjects and Methods

Fifty-eight chronically hospitalized elderly patients aged 65-96 (mean \pm SD: 80 \pm 6) without diseases primarily affecting the skeletal system were randomly divided into three groups of similar age and lumbar spinal bone density. Each patient was assigned to one of the three groups according to the date of admission: Group A. 20 subjects aged 50 ± 6 (mean \pm SD), Group B, 18 subjects aged 83 ± 4 , and Group C, 20 subjects aged 79 ± 9 . Excluded were 24 patients with severe compression fracture-compression or fractures-or marked osleophyle formation in L2-L1 as well as severe calcification of abdominal aorta interfering with accurate measurement. Degree of activity was classified into three grades: 3 for freely walking around without assistance, 2 for walking around with assistance, and 1 for being confined to wheelchair or bed. Group A consisted of 35% with activity level 3, 35% with 2, and 30% with 1 (mean 2.05 ± 0.80 SD); Group B 33, 28, and 39% (mean 1.94 ± 0.84); and Group C 20, 55, and 25% (1.95 ± 0.66), respectively. Mean serum 25(OH)vitamin D levels were 11.3 ± 3.1, 10.7 \pm 2.1, and 10.1 \pm 1.2 ng/ml in Groups A, B, and C, respectively, each group exhibiting mild vitamin D deficiency expected in elderly hospitalized patients. The changes of lumbar BMD in the same supplement group with different degree of activity were generally indistinguishable.

All patients were under regular hospital diet containing approximately 600 mg calcium/day. In addition, $\sin \sigma$ 6 either of the three kinds of indistinguishable capsules were given daily in three divided doses after each meal. The three kinds of capsules contained 150 mg Ca as AAA Ca for Group A, 150 mg Ca as CaCO₃ (precipitated calcium carbonate, Japanese Pharmacopeia) and for Group B, a placebo containing no Ca for Group C. The three doses provided 900 mg/day Ca supplement for Groups A and B and nothing for Group C. At the end of the 24-month period, supplements in Groups B and C were switched to AAA Ca, and Group A was kept on the same supplement to continue the observation for 6 more months.

Lumbar spine BMD (L_{2-4}) and midradial BMD at the junction of the middle and distal one-third site was measured with dual energy X-ray absorptiometry (DXA) by DPX (Lumar) before the beginning of the trial and every 3 months for 1 year and every 6 months after that. Coefficient of variation was 1.8% for lumbar BMD and 2.8% for midradial BMD on 10 repeated measurements of the same subject on different days. Midradial BMD was not

Table ia. Changes of lumbar bone mineral density

Group	A	B	С
Betore	0.625 ± 0.134	0.615 ± 0.134	0.623 ± 0.176
	(19)	(17)	(20)
3M	0.637 ± 0.133	0.608 ± 0.145	0.617 ± 0.187
	(17)	(17)	(20)
óМ	0.569 ± 0.135	0.596 ± 0.149	0.616 ± 0.200
	(15)	(13)	(17)
9M	0.652 ± 0.139	0.581 ± 0.127	0.620 ± 0.181
	(14)	(12)	(11)
12M	0.657 ± 0.137	0.599 ± 0.116	0.634 ± 0.107
	(13)	(10)	(6)
18M	0.656 ± 0.094	0.643 ± 0.100	0.609 ± 0.149
	(5)	(7)	(5)
24M	0.674 ± 0.119	0.624 ± 0.136	0.633 ± 0.182
	(5)	(6)	· (7)
30M	0.722 ± 0.037	0.665 ± 0.078	0.691 ± 0.151
	(4)	(4)	(6)

M = month

Changes of lumbar spine BMD, L_2-L_4 G/cm₂ (mean ± SD) through the test period in Group A supplemented with 900 mg/day calcium as AAA Ca, Group B supplemented with 900 mg/day calcium as CaCO₃, and Group C not supplemented with calcium, up to the 24th month, when 900 mg/day calcium as AAA Ca replaced CaCO₃ in Group B and placebo in Group C. In the lower part of the Table, the courses of changes of each value expressed as ratios to the individual basal value before the beginning of the study or rates of changes are shown. The number of samples for each set is given in parenthesis

measured at the 30th month, since a change of software made it impossible to compare the newly obtained values with the previous ones.

Second morning urine samples were obtained every month and the mean over each 6-month period was used to represent this period. Blood samples were obtained for serum alkaline phosphatase measurement every month, and the mean over each 6-month period was used to represent the period. Blood samples for PTH and calcitonin measurement were obtained in the middle of the study period 12 months after the beginning of the study when each group was on its respective supplement, and at 27 months after the beginning of the study when all groups were receiving AAA Ca—for 27 months in Group A and 3 months in Groups B and C. Serum intact PTH was measured by immunoradiometric assay (Nichols), midportion PTH by radioimmunoassay using the antibedy raised by Slatopolsky et al. in the chicken (Yamasa), and serum calcitonin by radioimmunoassay.

Data were statistically analyzed by analysis of variance (ANOVA) using Statview 4.02 system by Fisher's PSLD, Sheffe. and Bonferroni-Dunn method. Fisher's PSLD was used for multiple comparison with a constant variance, Sheffe's method was used to compensate for different sample sizes among the groups, and Bonferroni-Dunn's method for correction of the risk level. The results of measurement were expressed in absolute values and also as ratios to each individual basal value at the beginning of the study or the rates of changes, to correct for the variability of data possibly because of the high age of the test subjects. Consequently. the lower half of Tables 1 to 4 expressing the mean and SD of the ratios to each basal value or rates of changes were not calculated from the mean and SD of absolute values shown in the upper half of the respective Tables. The number of samples incvitably decreased progressively in each group because of the long study period and the high age of the test subjects. PIH and CT values were compared on the same subjects during the use of different supplements in each group and after switching the supplement to AAA Ca in all the groups.

The study was approved by the Institutional Review Board of Katsuragi Hospital. Informed consent was obtained from each patient who participated in the study.

Table 1b. Changes of the ratios of lumbar spine BMD to the basal value

			and the second secon
ЗМ/В	100.4 ± 3.5	98.5 ± 3.7	98.4 ± 4.6
	(17)	(17)	(20)
6M/B	101.1 ± 4.2	97.1 ± 4.3	97.2±6.7ª
	(15)	(13)	(17)
9M/B	100.6 ± 4.2^{b}	97.8 ± 4.0	$94.7 \pm 6.5^{\circ}$
	(14)	(12)	(11)
12M/B	$101.9 \pm 4.0^{\circ}$	98.0 ± 5.3	96.3 ± 7.1°
	(13)	(10)	(6)
18M/B	$103.3 \pm 3.8^{\prime\prime}$	98.9 ± 1.9	94.3±7.5ª
	(5)	(7)	(5)
24M/B	103.2 ± 3.8°	100.6 ± 6.2	96.6±4.5
	(5)	(6)	(7)
30M/B	101.8 ± 5.5	100.7 ± 9.6	99.1 ± 5.4
	(4)	(4)	(6)

Significant at P < 0.05 by ANOVA by Fisher's PSLD

 $^{*}P = 0.0460$ also significant by Bonferoni-Dunn method $^{*}P = 0.0050$ also significant by Sheff(and Bonferroni-Dunn

methods $^{\circ}P = 0.0354; {}^{\circ}P = 0.0083; {}^{\circ}P = 0.0434$

Results

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Lumbar spine BMD (L_2-L_4) decreased in Group C to 96.6 $\pm 4.5\%$ of the basal value at the 24th month, but increased to 103.2 $\pm 3.8\%$ in Group A. The ratios to the basal value were significantly higher in Group A than in Group C between the 6th and 24th months, as shown in Table 1. No significant difference, however, was found between Group B and Group C. In the 30th month of the study, 6 months after switching to AAA Ca in all groups, the value in Group C increased and no significant difference was any longer found among the three groups. Radial BMD was preserved in Group A but tended to fall in Groups B and C (Table 2).

Morning urinary calcium/creatinine ratio decreased from the basal level significantly in Group A after 18 months and in Group B after 12 months, but not as remarkably in Group C (Table 3). The ratio to the basal level, however, significantly declined only in Group A, from 1-7M/B to 19-24M/B and 25-30M/B, after an initial rise. Urinary Ca/Cr seemed to fall in Groups B and C in the 25-30th months after CaCO₃ or placebo was switched to AAA Ca, but this was not statistically significant. Serum alkaline phosphatase decreased in Group A more remarkably than in C. As shown in Table 4, the ratio to the basal value was significantly lower in A than in C at 1-6 and 19-24 months. These differences again disappeared after 6 months of AAA Ca

Although PTH was not measured at the beginning of the study, both intact and midportion PTH was significantly lower, and calcitonin higher. in Group A but not in Group B than in Group C at the 12th month from the beginning of the study. After AAA Ca was given in all the groups, intact PTH in Group C showed a significant fall with disappearance of the significant difference from Group A, as shown in Table 5.

Discussion

Oyster shell heated in vacuo was prepared by heating powdered oyster shells at reduced oxygen concentration at approximately 900°C. Though the original oyster shell mainly

Table 2. Changes of radial BMD

Group	A	В	С					
Before	0.456 ± 0.088	0.437 ± 0.087	0.501 ± 0.130					
	(18)	(18)	(19)					
ЭM	0.449 ± 0.092	0.429 ± 0.085	0.498 ± 0.122					
	(18)	(18)	(18)					
6M	0.444 ± 0.116	0.449 ± 0.078	0.493 ± 0.119					
	(13)	(11)	(14)					
9M	0.441 ± 0.093	0.445 ± 0.120	0.504 ± 0.151					
	(14)	(13)	(8)					
12M	0.439 ± 0.089	0.453 ± 0.106	0.463 ± 0.122					
	(13)	(10)	(8)					
18M	0.432 ± 0.114	0.477 ± 0.098	0.438 ± 0.122					
	(9)	(8)	(5)					
24M	0.476 ± 0.0051	0.448 ± 0.023	0.473 ± 0.040					
	(6)	(3)	(5)					
3M/B	98.3 ± 4.4	98.6 ± 7.7	97.4 ±5.9					
	(18)	(18)	(19)					
6M/B	98.1 ± 7.4	98.9 ± 7.3	95.9 ± 5.8					
	(13)	(11)	(14)					
9M/B	98.5 ± 5.6	97.0 ±9.7	96.5 ±4.8					
	(14)	(13)	(8)					
12M/B	99.4 ± 5.3	97.7 ± 8.2	97.1 ± 6.3					
	(13)	(10)	(8)					
18M/B	100.3 ± 4.6	98.0 ± 9.8	97.3 ± 6.5					
	(9)	(8)	(5)					
24M/B	100.5 ± 5.7	98.8 ± 3.0	97.0 ± 3.3					
	(6)	(3)	(5)					

Changes of the radial BMD measured by DPX at the junction of distal and middle one-third (RBMD g/cm² \pm SD) in Group A supplemented with 900 mg calcium as AAA Ca. Group B supplemented with 900 mg calcium as CaCO₃, and Group C supplemented with placebo containing no calcium up to the 24th month. In the second part of the Table, changes of the values are expressed as percentages of the baseline value prior to the test. Change of the software precluded comparable measurement at the 30th month. Numbers in parenthesis indicate sample numbers.

contains calcium carbonate, the oyster shell heated in vacuo showed a characteristic lamellar crystalline structure distinct from either calcium carbonate or calcium oxide, its final oxidation product. It may represent calcium oxide in a peculiar spacial arrangement, maintaining the ready solubility and bioavailability of calcium oxide without its irritability [1].

This oyster shell heated in vacuo was found to contain a trace amount of amino acids despite the exposure to a high temperature of 900°C: 0.012 mg/10 g serine, 0.008 mg/10 g glycine, 0.018 mg/10 g proline, and 0.017 mg/10 g leucine. AAA Ca was prepared by adding scawced preparation similarly heated at 900°C containing the same order of quantities of histidine, tyrosine, and valine in addition to oyster shell heated in vacuo.

In the present study, AAA Ca was found to increase lumbar spine BMD significantly better than the placebo, but the effect of the same amount of Ca supplied as CaCO₃ was not significant over placebo. Midradial BMD showed a similar but less pronounced change, maintenance at the initial level in Group A, and a mild decrease in Group B and further decrease in Group C. Morning urine Ca/Cr mainly reflects bone resorption, since the contribution of the absorbed calcium is expected to be minimal at this time. In these elderly subjects, factors such as degree of exercise, changes of fluid intake, and decline of renal function may

Page 3

Table 3a. Changes of urinary Ca/Cr ratio

Groups	A	B	C .
Before	0.344 ± 0.229	0.399 ± 0.251	0.328 ± 0.449
1-6M	(19) 0.309 ± 0.162	(18) 0.322 ± 0.140	(19) 0.297 ± 0.213
	(18)	(17)	(16)
7–12M	0.322 ± 0.170	$0.285 \pm 0.129^{\circ}$	0.254 ± 0.190
	(16)	(15)	(14)
13–18M	0.236 ± 0.159 (13)	0.223 ± 0.127^{h} (11)	0.242 ± 0.072 (8)
19-24M	$0.177 \pm 0.093^{\circ}$	0.216 ± 0.087^{4}	0.197 ± 0.105 (8)
2530M	(12) 0.173 ± 0.115⁼ (10)	(9) 0.179 ± 0.087 ^c (9)	(3) 0.174 ± 0.0083

Course of changes of morning urinary calcium/creatinine ratio in Group A supplemented with 900 mg/day calcium as AAA Ca, Group B supplemented with 900 mg/day calcium as CaCO₃ and Group C given placebo not containing calcium for 24 months. After 24 months. CaCO₃ and placebo in Groups B and C were replaced with 900 mg/day calcium as AAA Ca. Mean and SD of 6 monthly data were used to represent the overall trend during this period. In the second part of the Table, each value expressed as percentages of the basal pre-test value was similarly summarized. Numbers in parenthesis indicate sample numbers ANOVA by Fisher's PSLD

Difference from the basal pretest value was significant at ${}^{a}P = 0.0474$; ${}^{b}P = 0.0057$; ${}^{c}P = 0.0385$; ${}^{d}P = 0.0071$; ${}^{e}P = 0.227$; ${}^{f}P = 0.0013$ also significant by Bonferroni-Dunn method

Table 3b. Changes of the ratios to the basal value of urinary Ca/Cr

Groups	A	B	С		
1-6M/B	1.055 ± 0.552 (18) ²⁰	0.936 ± 0.429	1.135 ± 0.425 (16)		
7–12M	1.098 ± 0.499	0.972 ± 0.663	0.928 ± 0.420		
	(16)	(15)	(14)		
13—18M	0.755 ± 0.292 (13)	0.754 ± 0.462 (11)	1.044 ± 0.524 (8)		
19-24M	0.710 ± 0.456	0.738 ± 0.399	0.868 ± 0.421		
	(12)"	(9)	(8)		
2530M	0.722 ± 0.485	0.606 ± 0.327	0.734 ± 0.524		
	(10) ^h	(9)	(9)		

B = Significantly different by ANOVA with Fisher's PSLD *P = 0.0417 and *P = 0.0373, respectively

influence urinary excretion of calcium and creatinine, so that the interpretation of these data requires additional caution. Serum alkaline phosphatase reflects bone turnover and is known to rise in osteoporosis. Decrease of these parameters may therefore indicate inhibition of bone resorption which may be pronounced in elderly subjects with low calcium intake and poor intestinal absorption of calcium due to vitamin D deficiency. Serum intact and midportion PTH indicating the degree of calcium deficiency and predicting the degree of bone resorption tended to be lower on supplementation with AAA Ca, with a significant fall in Group C after switching from placebo to AAA Ca, suggesting PTH suppression and decreased bone resorption in response to effective calcium supplement. Improvement of lumbar BMD on switching to AAA Ca from placebo, along with a fall of serum PTH in Group C, appears to confirm the effect Exhibit 5

Table 4. Changes of serum alkaline phosphatase

Groups	A	B	C
Before	9.1 ± 3.9	8.9± 2.7	8.2± 2.6
	(19)	(16)	(17)
1-6M	8.2 ± 3.4	8.2 ± 2.5	8.6 ± 2.9
	(19)	(16)	(17)
7-12M	8.6 ± 3.5	7.2 ± 2.0	8.1± 1.9
	(13)	(10)	(7)
13–18M	7.8 ± 2.8	7.2 ± 2.2	8.3 ± 2.0
	(13)	(11)	(ឪ)
19-24M	7.1 ± 2.7	6.9 ± 1.9	8.4± 1.3
	(10)	(11)	(6)
2530M	6.3 ± 1.5	6.5 ± 1.4	7.8± 2.5
	(9)	(8)	(6)
1-6M/B	91.9 ± 19.6≈	93.7 ± 19.9	105.7 ± 16.4°
	(19)	(16)	(17)
7-12M/B	98.5 ± 42.3	98.2 ± 26.2	108.6 ± 27.0
	(13)	(10)	(7)
13–18M	89.6 ± 27.8	91.3 ± 28.1	108.4 ± 34.2
	(13)	(11)	(8)
19-24M	79.1 ± 22.2 ^b	89.2 ± 30.3	109.8 ± 29.8°
	(10)	(11)	(6)
25-30M	84.7 ± 3.52	93.0 ± 22.2	90.2 ± 32.4
	(9)	(8)	(6)

Course of alkaline phosphatase (King-Armstrong units, mean \pm SD) in Group A supplemented with 900 mg/day calcium as AAA Ca. Group B supplemented with 900 mg/day calcium as CaCo₃, and Group C not supplemented with calcium, up to 24 months. After this period, all three groups were supplemented with 900 mg/day calcium with AAA Ca. In the second part of the Table, each value expressed as percentages of the individual basal pretest value is summarized. Numbers in parenthesis indicates sample numbers.

Significant difference between ${}^{a}P = 0.313$; ${}^{b}P = 0.0402$ by ANOVA with Fisher's PSLD

Table 5. (Changes of	serum	parathyroid	hormone a	and calcitonin
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Groups	A	В	С		
iPTH (test)	26± 9°	38± 13	47± 1320		
(,	(7)	(6)	(8)		
iPTH (after)	22 ± 7	33 ± 17	$24 \pm 10^{\circ}$		
•	(7)	(6)	(8)		
mPTH (test)	487 ± 85°.0	755 ± 200 ⁻	825 ± 268^{4}		
	(7)	(6)	(8)		
mPTH (after)	353 ± 137° ±	622 ± 133°	$634 \pm 235'$		
	(7)	(б)	(8)		
CT (test)	27 ± 5 ⁸	23 ± 5	18± 5 ⁵		
	(7)	(6)	(6)		
CT (after)	21 ± 4	20 ± 3	18± 4		
	(7)	(6)	(6)		

Serum intact parathyroid hormone (iPTH), midportion parathyroid hormone (mPTH), and calcitonin (CT) in pg/ml \pm SD. During the first 24 months, Group A was supplemented with 900 mg/day calcium as AAA Ca, Group B with 900 mg calcium as CaCO₂ and Group C with placebo. After this period, all Groups were supplemented with 900 mg calcium as AAA Ca as in Group A. Values at the 12th month of the study (test) and 6 months after the switch of the supplements (after) are shown. Numbers in parenthesis indicate sample numbers.

Significant differences by Fisher's PSLD

 ${}^{\circ}P = 0.0024; {}^{\circ}P = 0.0060; {}^{\circ}P = 0.0122; {}^{\circ}P = 0.0015; {}^{\circ}P = 0.0122; {}^{\circ}P = 0.0015; {}^{\circ}P = 0.0022$

Page 4

of AAA Ca Calcium carbonate also appeared to decrease urinary calcium excretion, but the ratio to the basal level failed to change significantly from the level in the first 6 months, unlike AAA Ca.

The reason for the good bioavailability of AAA Ca suggested in the present study remains to be elucidated. Though certain amino acids are known to increase intestinal absorption of calcium, the amount of amino acids found in AAA Ca was much less than the level at which any such action of amino acids is expected [6, 7]. Since serum 25(OH)-vitamin D values were low in each group and the degree of activity was also similar, the property of calcium supplement seems to be dominant.

Calcium supplement increased bonc density or inhibited the age-bound bone loss [8-13], but also failed to prevent postmenopausal bone loss completely [14, 15]. Dawson-Hughes [16] pointed out the need for supplement of about 1000 mg or more of calcium to see a positive effect and also showed that the effect depended on the years after menopause. Cumming [17] reviewed trials of calcium supplement, pointing out better effects of calcium supplement in premenopausal women with low calcium intake. Since estrogen itself favors calcium absorption, the presence of estrogen may provide a better environment for the effect of calcium supplementation. Recently, Elders et al. [18] showed a positive effect of long-term calcium supplement in perimenopausal women. However, none of these studies so far reported concentrated on elderly women as in the present study. presumably because of difficulties accompanying such studies on subjects who are extremely age. In patients in this age range, especially those in the institutions, some vitamin D deficiency is inevitable and the intrinsic bioavailability of the calcium preparation appears to be crucial to achieving a positive effect.

References

- Fujita T. Fukase M. Nakada M, Koishi M (1988) Intestinal absorption of oyster shell electrolysate. Bone Miner 4:321-327
- Yoshimoto Y, Tsukamoto T, Fukase M, Imai Y, Fujii T, Nakai M, Fujimori A. Ohno K. Ikeda K. Yamada H, Nishikawa M, Yamamoto Y, Kitazawa R, Fujita T (1990) Bioavailability of oyster shell electrolysate. J Bone Miner Metab 8:87-90
- Fujita T, Fukase M, Miyamoto H. Matsumoto T, Ohue T (1990) Increase of bone mineral density by calcium supplement with oyster shell electrolysate. Bone Miner 11:85-91
- Fujita T (1993) Oyster shell electrolysate (AACa) with high biological availability. J Bone Miner Metab 11:S41-45
- Fukuda S (1993) Effects of active amino scid calcium: its bioavailability on intestinal absorption, osteoporosis and removal of plutonium in animals. J Bone Miner Metab 11:547-51
- Lee YS. Noguchi T. Naito H (1983) Intestinal absorption of calcium in rats given diets containing case or amino acid mixture: the role of case in phosphopeptides. Br J Nutr 49:67– 76
- Orimo H, Fujita T, Goto Y, Yoshikawa M (1967) Mechanism of hypercalcemic effect of I-valine in parathyroidectomized rats. Endocrinol Jpn 80:200-202
- Polley JK, Nordin BEC, Bughurst PA, Walker CJ, Chatterton BE (1987) Effect of calcium supplementation on forearm bone mineral density in postmenopausal women. J Nutr 117:1929– 1935
- Dawson-Hughes B, Dallas GE, Krall GE (1990) A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 323:878-883
- 10. Aloia JF, Vaswani A, Yeh JK. Ross PL. Flaster E. Dilnanian

FA (1994) Calcium replacement with and without hormone replacement therapy to prevent postmenopausal bone loss. Ann Intern Med 120:97-103

- Smith EL, Gilligan C, Smith PE. Sempos CT (1989) Calcium supplementation and bone loss in middle-aged women. Am J Clin Nutr 50:833-842
- 12. Elders P, Netelenbos J, Lips P, van Ginkel F, Khoe E, Leeuwenkamp O, Hackeng W, van der Stelt P (1991) Calcium supplementation reduces vertebral bone loss in perimeno-pausal women: a controlled trial in 248 women between 46 and 58 years of age. J Clin Endocrinol Metab 73:533-540
- Prince Ř, Smith M, Dick I, Price R, Webb P, Henderson N. Harris M (1991) Prevention of postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation and hormone-replacement therapy. N Engl J Med 325:1189-1195
- Riis B, Thomsen K, Cristiansen C (1987) Does calcium supplementation prevent postmenopausal bone loss? A doubleblind, controlled clinical study. N Engl J Med 316:173-177
 Nilas L, Christiansen C, Rodbro P (1984) Calcium supple-
- Nilas L, Christiansen C, Rodbro P (1984) Calcium supplementation and postmenopausal bone loss. Br Med J 289:1103– 1106
- Dawson-Hughes B (1991) Calcium supplementation and bone loss: a review of controlled clinical trials. Am J Clin Nutr 54:274S-280S
- Cumming RG (1990) Calcium intake and bonc mass: a quantitative review of the evidence. Calcif Tissue Int 47:194-201
- Elders PJM, Lips P, Netelenbos JC, van Ginkel FC, Khoe E, van der Vijgh WJF, van der Stelt PF (1994) Long-term effect of calcium supplementation on bonc loss in perimenopausal women. J Bone Miner Res 9:963-970

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Reappraisal of Katsuragi Calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture

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Abstract A prospective, double-blind, placebo-controlled study of the effect of supplementation with 900 mg/day of calcium, as active absorbable algal calcium (AAA Ca) or calcium carbonate (CaCO₃), on lumbar bone mineral density (BMD) carried out in elderly inpatients with osteoporosis at Katsuragi Hospital was re-evaluated in terms of the effects on vertebral fracture and spondylotic deformity. In addition to the already reported increase in lumbar BMD, AAA Ca was found to inhibit new occurrence of vertebral fracture. Intraindividual variations in L₁-L₄ BMD (expressed by the coefficient of variation, indicating the degree of spondylotic deformity, were also inhibited significantly in the group supplemented with AAA Ca (group A), but not in group B (supplemented with CaCO₃), from the level in the placebosupplement group (group C) after 18 months of supplementation. According to whole-body dual-energy X-ray absorptiometry (DXA) results in the first and second year of the study, whole body mass, lean content, and mineral content, expressed as a percentage of whole body mass, stayed unchanged, while increase of fat content was significantly inhibited in group A, but not in group B, from the level in group C. As to the regional distribution of bone mineral content, the second year/first year value for head bone mineral content was significantly decreased with AAA supplementation compared with placebo, but no significant difference was found between CaCO₃ and placebo supplementation. Changes in mineral distribution in the arms, trunk, and legs showed no significant differences among the three groups. In addition to increasing BMD and preventing fracture, AAA Ca, but not CaCO3, appears to inhibit the occurrence of spondylotic deformity and to decrease body fat content.

Key words osteoporosis · spondylotic deformity · fat mass · active absorbable algal calcium (AAA Ca) · dual-energy X-ray absorptiometry (DXA)

Introduction

A prospective, randomized, double-blind, placebocontrolled study was carried out to determine the effect of active absorbable algal calcium (AAA Ca) on osteoporosis in three groups of elderly patients hospitalized at Katsuragi Hospital, Osaka, Japan (Katsuragi Calcium Study) [1]. The three groups received daily supplementation with: (1) 900 mg calcium as AAA Ca (group A), (2) 900 mg calcium as calcium carbonate (CaCO₃, group B), and (3) starch placebo containing no calcium (group C). The supplement was given daily in six capsules (indistinguishable among groups) over a period of 2 years. Lumbar bone mineral density (BMD), measured by dual-energy absoptiometry (DXA) in the anterior-posterior direction was significantly higher in group A (supplemented with AAA Ca) than in the placebo-supplemented group C, whereas no significant difference was found between group B (supplemented with $CaCO_3$) and group C.

In the present study, the data for DXA of the lumbar spine were re-analyzed to calculate the intra-individual standard deviation (SD) and coefficient of variation (CV; SD divided by mean) of L_1-L_4 BMD to assess the development of spondylotic changes [2–5]. Lateral spine X-ray films taken before and after the study in groups A, B, and C were evaluated, and the intraindividual CV of the projected area of the L_1-L_4 vertebral bodies was calculated to detect new occurrence of fracture. Whole body DXA was performed in the first and second year of the study to follow changes in whole body mineral content and other parameters.

Subjects and methods

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Offprint requests to: T. Fujita (e-mail: fujita@katsuragi-hosp.or.jp) Received: January 8, 2003 / Accepted: May 9, 2003 The Katsuragi Calcium Study was conducted in 58 hospitalized elderly women randomly divided into three groups of similar age, lumbar BMD, and grade of daily

Page 1

physical activity. All patients were receiving a regular hospital diet containing approximately 600 mg Ca daily. Group A, consisting of 20 subjects with a mean age of 80 ± 6 years (mean \pm SD) was given 900 mg/day Ca supplement as AAA Ca; group B, consisting of 18 subjects aged 83 ± 6 years, was given 900 mg/day Ca supplement as precipitated CaCO₃ (Japanese Pharmacopeia), and group C, consisting of 20 subjects aged 79 ± 9 years, was given placebo containing no Ca. Each supplement was contained in six indistinguishable capsules, two to be taken after each meal daily, over a period of 2 years, under a strict double-blind principle.

In addition to the mean L_1-L_4 BMD, measured by DXA in the anterior-posterior direction (LBMD), intra-individual variation of L_1-L_4 BMD was evaluated by calculating the SD and coefficient of variation (CV; SD divided by the mean L_1-L_4 BMD) at 3, 6, 9, 12, 18, and 24 months after the beginning of the study, using a Lunar DPX instrument (Madison, WI, USA) [2-5]. Subjects with a marked loss of vertebral height within L_1-L_4 , suggesting compression fracture, were excluded prior to entry.

Vertebral fracture was assessed before and after the trial, based on lateral X-ray films of the thoracic and lumbar spine, in six, seven, and six subjects in groups A, B, and C, respectively. New appearance in a decrease in either the middle or anterior vertebral height by 20% or more, compared to the posterior height of the same vertebra, or the one immediately adjacent, was defined as the occurrence of vertebral fracture. The CV of the projected area of L_1-L_4 vertebral bodies was also calculated to detect vertebral compression fracture expressing itself as an increase in the intra-individual variation of the projected areas.

Whole body DXA was performed in the first and second year of the study (6 and 18 months after the beginning of the study) to measure the whole body mass, lean content expressed as a percentage of the whole body mass; mineral content expressed as a percentage of the whole body mass; and fat content expressed as a percentage of the whole body mass. Distribution of regional mineral content in the head, arms, trunk, and legs was also calculated, as a percentage of the whole body mineral content [6]. Because no whole body measurement was performed prior to the beginning of the study, the value for second year/first year (%) was used as an index of the change.

Statistical analysis, consisting of multiple comparison with analysis of variance and Fisher's protected least significant difference (PLSD) test and the χ^2 test was carried out on Statview 5.0 (Abacus Concepts, Berkley, CA, USA).

Informed consent, given by the patients or their families, was obtained, and the study was approved by the Institutional Review Board of Katsuragi Hospital.

Results

As shown in Fig. 1, the mean L_1-L_4 -BMD started to rise 6 months after the beginning of the study in group A (supplemented with AAA Ca), suggesting restoration of the decreased bone mass, leading to a significant difference from group C (given placebo) throughout the rest of the study period, as already reported, whereas group B (supplemented with $CaCO_3$) showed no significant difference from group C (supplemented with placebo) [1]. Intra-individual variation of L_1-L_4 BMD, expressed as CV (shown in Fig. 2), on the other hand, was significantly suppressed in group A (supplemented with AAA Ca) from the level in the placebosupplemented group C after 18 months, suggesting inhibition by AAA Ca supplementation, of the development of spondylotic changes. Group B (supplemented with CaCO₃) did not exhibit a significant difference from either group A or group C in mean BMD or intraindividual variation. The SD of L₁-L₄ BMD showed no significant difference among the three groups, as shown in Fig. 3.

In the six subjects in group A (supplemented with AAA Ca) for whom lateral spine X-ray films were examined for the occurrence of new fracture, no new vertebral fracture occurred during the study period of 2 years, whereas, in two of the seven subjects in group B

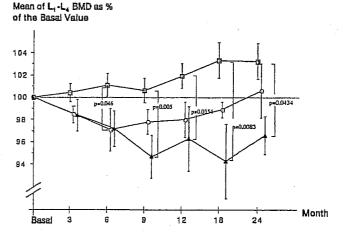


Fig. 1. Mean lumbar bone mineral density $(BMD; L_1-L_4)$, expressed as a percentage of the basal value on the ordinate and time in months on the *abscissa*, in the Katsuragi Calcium Study, as already reported. Group A, supplemented with active absorbable algal calcium (AAA Ca) is shown by squares; group B, supplemented with CaCO₃, as circles; and group C, supplemented with placebo, as triangles. Increase of the mean lumbar BMD was significantly greater in group A than in group C after six months. No significant difference was found between group B and group C or between group B and group A. Multiple comparison was done by analysis of variance and Fisher's PLSD. Mean \pm SEM

Exhibit 6

Page 2

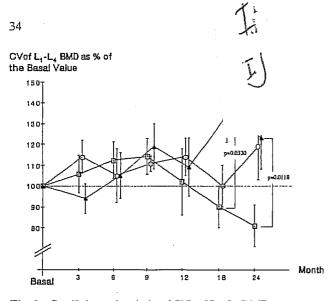


Fig. 2. Coefficient of variation (CV) of L_1-L_4 BMD, expressed as a percentage of the basal value on the *ordinate* and time in months on the *abscissa*, in the Katsuragi Calcium Study. Group A, supplemented with AAA Ca, is shown by *squares*; group B, supplemented with CaCO₃, as *circles*; and group C, supplemented with placebo, as *triangles*. After 18 months, changes in the CV of L_1-L_4 BMD, expressing the degree of spondylotic deformity over the basal level, were significantly greater in group C than in group A, suggesting effective suppression of spondylotic deformity by AAA Ca. No significant difference was found between group B and group C or between group B and group A. Multiple comparison was done by analysis of variance and Fisher's PLSD. Mean \pm SEM

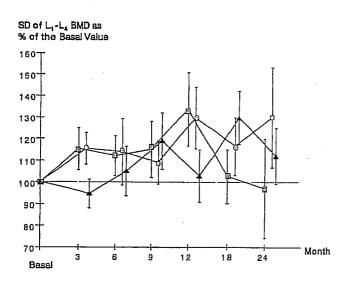


Fig. 3. Intra-individual SD of L_1-L_4 BMD, expressed as a percentage of the basal value on the *ordinate* and time in months on the *abscissa*, in the Katsuragi Calcium Study. Group A, supplemented with AAA Ca, is shown by *squares*; group B, supplemented with CaCO₃, as *circles*; and group C, supplemented with placebo, as *triangles*. No significant difference was found among the three groups at any time. Multiple comparison great done by analysis of variance and Fisher's PLSD. Mean \pm SEM

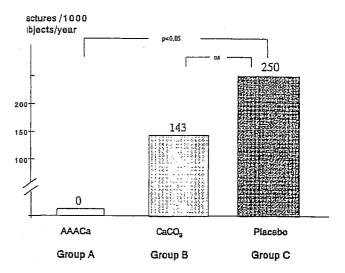
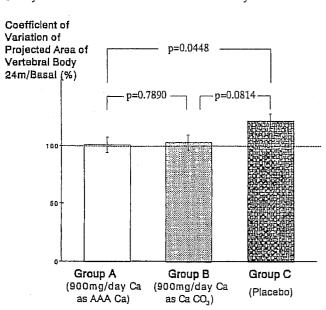
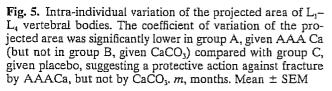


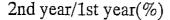
Fig. 4. Frequency of occurrence of new fractures during the 2year study period in the Katsuragi Calcium Study. Open bar represents group A, supplemented with AAA Ca; shadowed bar, group B, supplemented with CaCO₃, and closed bar, group C, supplemented with placebo. According to the χ^2 test, the frequency of fractures was significantly greater in group C (250 patients/1000 years) than in group A (0 patient/1000 years; P < 0.05), but no significant difference (ns) was found between group B (143 patients/1000 years) and group C

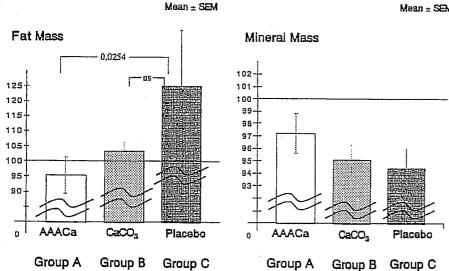
(supplemented with CaCO₃) and three of the six subjects in group C (supplemented with placebo) similarly studied, a vertebral fracture was sustained during the same period, making the yearly incidence of new fracture per 1000 subjects 0 for group A, 143 for group B, and 250 for group C, the difference between groups A and C being significant, by the χ^2 test, at P < 0.05, as shown in Fig. 4. No significant difference was found between group B (supplemented with CaCO₃) and group C (supplemented with placebo). The CV of the projected area of the vertebral bodies was significantly higher in group C (given placebo) than in group A (given AAA Ca), suggesting protection by AAA Ca from the occurrence of changes in the projected area of the vertebral bodies, whereas no such significant protection by CaCO₃ was noted, in view of the absence of a significant difference between groups B and C, as shown in Fig. 5.

On whole body DXA measurement in the first and second years of the study (shown in Fig. 6), no significant differences were found among the three groups as to changes from the first to the second year in body weight, total body mass, and whole body lean mass (expressed as a percentage of the total body mass). As to changes in fat mass, expressed as a percentage of the whole body mass, the first year/second year value in group A (supplemented with AAACa) was significantly lower than that in group C (supplemented with









placebo), indicating an inhibition of fat accumulation by AAA Ca supplementation. However, no significant difference was found between group B (supplemented with CaCO₃) and group C (supplemented with placebo). The change in total mineral mass as a percentage of the total body mass suggested a slightly smaller loss in group A than in the other groups, without significant difference (Fig. 7).



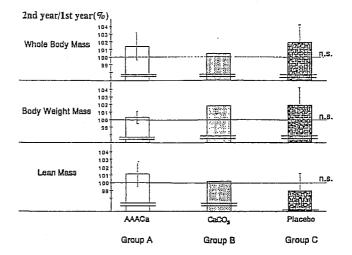


Fig. 6. Whole body mass is shown in the upper panel, body weight in the *middle panel*, and whole body lean mass in the lower panel, expressed in terms of second year/first year values (%). Open bars represent group A, supplemented with AAA Ca; shadowed bars, group B, supplemented with CaCO₃; and closed bars, group C, supplemented with placebo. No significant differences were found among the three groups, and all values remained almost constant

Mean ± SEM

Fig. 7. Whole body mineral mass is shown in the right panel and whole body fat mass is shown in the in the *left panel*, with the second year value expressed as a percentage of the value in the first year. Open bars represent group A, supplemented with AAA Ca; shadowed bars, group B, supplemented with CaCO₃; and closed bars, group C, supplemented with placebo. While the changes in the total mineral mass were not significantly different among the three groups, increase of fat mass was significantly greater in group C, supplemented with placebo, than in group A, supplemented with AAA Ca. No significant difference was found between groups B and C

As to the regional distribution of bone mineral content, AAA Ca, but not CaCO₃, supplementation significantly decreased the bone mineral content of the head, expressed as a percentage of the whole body mineral content, over placebo supplementation, while changes in the mineral content of the arms, trunk, and legs were not significantly different among the three groups (Fig. 8).

36

T. Fujita et al.: AAACa on vertebral deformity

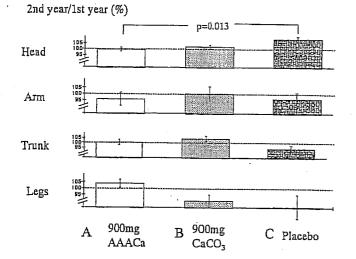


Fig. 8. Regional distribution of bone mineral content in head, arms, trunk, and legs; second year values are expressed as percentages of the first year values. Open bars represent group A, supplemented with AAA Ca; shadowed bars, group B, supplemented with CaCO₃; and closed bars, group C, supplemented with placebo. The head bone mineral content was significantly decreased in group A compared with group C, but no significant difference was found between groups B and C. No significant difference was found among the three groups as to the changes in the bone mineral content of the arms, trunk, or legs

Discussion

Active absorbable algal calcium (AAA Ca), produced by heating oyster shell and seaweed in vacuo, is readily absorbed from the intestine [7], and significantly increased lumbar BMD in elderly women over the level in the placebo-supplemented group in a 2-year prospective, randomized double-blind study (Katsuragi Calcium Study) [1], whereas supplementation with the same amount of calcium, as CaCO₃, showed an effect that was not significantly better than the placebo. Peripheral computed tomography of the distal radius made it possible to detect the effect of AAA Ca in increasing trabecular BMD at the distal radius in a double-blind comparison with CaCO₃ and placebo in postmenopausal women in a 4-month period [8,9].

In the present study, DXA data on the lumbar spine from the Katsuragi Calcium Study were reanalyzed to assess the degree of spondylotic deformity, expressed as intra-individual coefficient of variation of L_1-L_4 BMD. Lateral X-ray pictures of the thoracic and lumbar spine were examined to detect the occurrence of new fracture, along with calculation of intra-individual variation of the projected area of the L_1-L_4 vertebral bodies. Whole body DXA data obtained in the first and second year of the Katsuragi Calcium Study were also analyzed to define the effect of AAA Ca on total body mineral content, lean content, and fat content in comparison with the effect of $CaCO_3$ and placebo.

Although lateral spine X-ray films at the beginning and end of the study were available for only a small number of subjects in each group, the significantly lower second year/first year (%) value for new vertebral fracture in group A (supplemented with AAA Ca) than in group C (given placebo) tends to support the protective action of AAA Ca against fracture through an increase of lumbar BMD, whereas supplementation with CaCO₃ showed no significant protective effect over placebo [2]. Compression fracture of the vertebra decreases the projected area of the vertebra most dramatically with a rise in the CV, but spondylotic deformity, even with osteophyte formation, is expected to increase the projected vertebral area only slightly. The significantly lower intra-individual CV of the projected area of the vertebral bodies in group A (given AAA Ca), but not in group B (given CaCO₃) compared with group C (given placebo) also supports the protective action of AAA Ca but not CaCO₃ on vertebral fracture (Fig. 5).

The intra-individual variation of L1-L4-BMD, expressed as the CV, was suggested to be one of the manifestations of spondylotic and osteoarthritic deformity [2-6], based on a high correlation with X-ray findings of spondylosis deformans, with both conditions increasing markedly with age, although some minor influence of vertebral compression deformity on the intra-individual variation of lumbar BMD cannot be ruled out. Lumbar spine BMD started to increase from around the sixth month of supplementation in the present study, and intra-individual variation of L1-L4-BMD (CV; SD expressed as a percentage of the mean), also increased, somewhat later than BMD in group C over group A, whereas it did not increase in group B. SD itself, which was strongly dependent on the mean, did not change in group A despite the rise in mean BMD. In the analysis of the SD and CV of the lumbar spine BMD, a high dependency of SD on the mean BMD was found, but the CV (corrected SD expressed as a percentage of the mean) is free of such dependence. Both the CV and Xray findings of spondylotic deformity were found to increase in parallel with age in males and females, but the SD itself increased with age only in males (with a relatively mild change in the mean BMD with age) and not in females, with a marked fall of mean BMD being shown with age. The intra-individual CV but not the SD of lumbar BMD thus appears to reflect the degree of spondylotic change [6].

Spondylosis deformans and osteoarthritis were once thought to be distinctly different and even incompatible with osteoporosis both etiologically and sementically. Nevertheless, the coexistence of these two diseases is rather frequent, especially in postmenopausal women with osteoporosis and osteoarthritis of the knee. Both

1. Fujita et al.: AAACa on venebrai derorinity

degenerative joint disease and osteoporosis represent major causes of incapacitating backache and joint pain, which are a distinct threat to the quality of life in the aging population. In DXA of the lumbar spine, a decrease in BMD is naturally a gold standard for the diagnosis of osteoporosis, whereas an artifactual increase in lumbar spine BMD is frequently encountered in subjects with spondylosis deformans or osteoarthritis of the spine, because of secondary changes such as osteophyte formation, eburnation, and localized hyperostosis; this could explain a possible source of misconception on the "incompatibity" of osteoporosis and osteoarthritis. These two groups of diseases, indeed, may be based on a common etiology of calcium deficiency [10,11]. Calcium deficiency, due to insufficient intake, decreased intestinal absorption, increased urinary loss, vitamin D deficiency (due to decreased renal calcitriol synthesis), estrogen deficiency, corticosteroid excess, and other causes prompts increased parathyroid hormone (PTH) secretion. PTH stimulates bone resorption and Ca release from bone and Ca entrance into cartilage along with excessive physical load. Increase of the Ca content of cartilage causes its hardening and susceptibility to physical stress, leading to the wearing out and subsequent disappearance of cartilage. The resulting direct bone-to-bone contact evidently causes many of the osteoarthritic and spondylotic changes.

The failure to achieve a significant increase in total body mineral content in 2 years of AAA Ca supplementation may be due to the predominant contribution of cortical bone to the total body mineral content. In the Katsuragi Calcium Study [1], radial cortical BMD also failed to increase during this period. Rather unexpectedly, a significant decrease in total body fat content relative to whole body mass was noted on supplementation with AAA Ca over against placebo-supplemented controls, but supplementation with CaCO3 caused no significant decrease in fat content from the level in the placebo group. Whole body mass, lean mass, and body weight remained relatively constant through the study period in each group. An increase of fat mass was reported to be associated with increased BMD through an increase of weight load, in part [12-14]. Because exercise tends to increase bone mass and decrease fat mass [15], it is conceivable that AAA Ca, by increasing the range of activity, acts like exercise to decrease fat mass. In obesity, on the other hand, Ca deficiency, secondary hyperparathyroidism, and increased intracellular free Ca in adipocytes may be present [16]. Readily absorbable AAA Ca is probably effective to minimize such fat accumulation due to secondary hyperparathyroidism, another example of the calcium paradox.

A significant decrease in the mineral distribution in the head portion, the only nonweight-bearing portion of the body, along with increases in other weight-bearing

or active parts, on supplementation with AAA Ca, but not CaCO₃, over that with placebo may also reflect an increase in the level of physical activity or some metabolic effect similar to such an increase in response to AAA Ca but not to CaCO₃. Age-related increases in head mineral content, with a tendency toward decreases in other body parts, especially in the legs, was reported and explained by decreasing muscle strength and physical activity during aging [6]. The decrease in head mineral content on supplementation with AAA Ca may therefore represent a process of skeletal rejuvenation by prompting physical activity or a metabolic enhancement that is similar to physical activity. The striking parallelism of these metabolic effects of AAA Ca (but not CaCO₃) over placebo suggests that AAA Ca may be more useful than CaCO₃ as a nutritional supplement.

References

- Fujita T, Ohue T, Fujii Y, Miyauchi A, Takagi Y (1996) Heated oyster shell-seaweed calcium (AAA Ca) on osteoporosis. Calcif Tissue Int 58:226-230
- Fujita T, Fujii Y, Miyauchi A, Takagi Y (2001) A double-blind placebo-controlled prospective study comparing active absorbable algal calcium (AAACa) with CaCO₂ on spinal fracture and spondylotic deformity. J Bone Miner Res 16 (Suppl 1):S288 (Abstract)
- Fujita T, Fujii Y, Goto B, Miyauchi A, Takagi Y (1999) Parallel advance and etidronate effect in osteoporosis and degenerative joint disease shown by intra-individual variation of lumbar spine BMD and peripheral computed tomography (pQCT). Bone 23 (Suppl 5):S597 (Abstract)
- Fujita T, Fujii Y, Miyauchi A, Takagi Y (2001) Intraindividual coefficient of variation of lumbar spine density as an index of spondylotic deformity. Bone 28 (Suppl 5):S173 (Abstract)
- 5. Fujita T, Fujii Y, Miyauchi A, Takagi Y, Ohgitani S (2000) Analgesic effect of etidronate in degenerative joint disease shown by inhibition of the fall of skin impedance caused by physical strain along with the decreased variation of spinal BMD. J Bone Miner Res 15 (Suppl 1):S235 (Abstract)
- Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y (2003) Intraindividual variation of lumbar bone mineral density as a measure of spondylotic deformity. J Bone Miner Metab 21:98-102
- Fujita T, Fujii Y, Morishita T, Inoue T (1999) Changes of regional distribution of bone mineral according to age, gender and physical activity. J Bone Miner Metab 17:217-213
- Fujita T, Fujii Y, Goto B, Miyauchi A, Takagi Y, Kobayashi S, Kamosita K, Mikuni N, Kurihara Y, Shirauchi I (2000) Increase of intestinal calcium absorption and bone mineral density by heated algal ingredient (HAI) in rats. J Bone Miner Metab 18:165-169
- Fujita T, Fujii Y, Goto B, Miyauchi A, Takagi Y (2000) Peripheral computed tomography (pQCT) detected short-term effect of AAA Ca (heated oyster shell with heated algal ingredient HAI): a double-blind comparison with CaCO₃ and placebo. J Bone Miner Metab 18:212-215
- Fujita T (1998) Degenerative joint disease: an example of calcium paradox. J Bone Miner Metab 16:195-205
- Fujita T, Palmieri GMA (2000) calcium paradox disease: calcium deficiency prompting secondary hyperparathyroidism and cellular calcium overload. J Bone Miner Metab 18:109–125
- Reid IR, Ames R, Evans MC, Sarpe S, Gambles G, France JT, Lim TJ, Cundy TF (1992) Determination of total body and re-

gional bone mineral density in normal postmenopausal women a key role for fat mass. J Clin Endocrinol Metab 75:45-51

- Reid IR, Plank LD, Evans MC (1992) Fat mass is an important determinant of whole body bone density in premenopausal women but not in men. J Clin Endocrinol Metab 75:779-782
- 14. Raven P, Cizza G, Bjamason NH, Thompson D, Daley M, Wasnich RD, McClung M, Hosking D, Yates AJ, Christiansen C (1999) Low body mass index is an important risk factor for low bone mass and increased bone loss in early postmenopausal

women. Early Postmenopausal Intervention Cohort (EPIC) Study Group. J Bone Miner Res 14:1622–1627

- Druznin B, Sussman KE, Eckek RH, Kao M, Yost T, Sherman N (1988) Possible role of cytosolic free calcium concentrations in mediating insulin resistance of obesity and hyperinsulinemia. J Clin Invest 82:1848-1852
- 16. Segal S, Lloyd S, Sherman N, Sussman KE, Druznin B (1990) Postprandial changes in cytosolic free calcium and glucose uptake in obesity and non-insulin-dependent diabetes mellitus. Horm Res 34:39-44

An interview with Takuo Fujita, M.D. President, Osteoporosis Foundation of Japan Founder, Calcium Research Institute of Japan

Dr Fujita, please tell us about your background

I am a physician, clinical investigator and radio technologist. I received my degree of Doctor of Medicine from the University of Tokyo in 1952. As a recipient of the Fulbright fellowship I continued my studies at the University of Buffalo from 1952 up to 1956. As one of the pioneers of calcium studies I studied calcium metabolism and bone disease at the University of Tokyo and at Kobé University.

Tell us of your current activities in calcium research

I am the president of the Japan Osteoporosis Foundation and director of the Calcium Research Institute so I am very active in every aspect of calcium studies, including patient studies and clinical investigations.

How many studies have you published on calcium?

Four hundred and twenty, all in peer review journals.

How long have you been researching calcium and osteoporosis?

About 46 years. I began in 1953 at the University of Buffalo Chronic Disease Research Institute. At that time I came in contact with a serious disease of calcium metabolism—kidney stones in patients with poliomyelitis (polio). I was actually led by a personal motive. At that time there was a great polio epidemics in this country and many young people —I remember many of them—suffered from acute poliomyelitis. What happened is, they suddenly lost use of their muscles. They became paralyzed and couldn't move their bones any more. All the calcium came out of the bone causing through the kidney in the urine. They formed huge kidney stones. The kidney lost its function and patients died of the kidney stones. This was very serious and moved me profoundly. I thought there must be something we could do to control calcium metabolism.

What is osteoporosis? How serious a disease is it?

Osteoporosis is weak, breakable, brittle bone, which occurs as a consequence of calcium loss from bone. Bone without calcium is very weak and if we don't take enough calcium, or if we lose too much, our bodies become calcium deficient. Since 99% of calcium in the body is in the bone, bone is the first part of the body to be affected.

Why is osteoporosis often considered a woman's disease?

Men also lose calcium, but women undergo a very dramatic event at the time of menopause. A <u>sudden decrease in estrogen (female hormone) brings menstruation to an end and triggers a</u> very rapid loss of bone-calcium. This is called post-menopausal osteoporosis. We all paid too much attention to this one event and we thought that post-menopausal osteoporosis was everything. That's why for so long we considered osteoporosis a women's disease. Certainly, it occurs more frequently in women, and earlier too. After the age of fifty, women are exposed to increased risk of osteoporosis, whereas men reach an equivalent risk factor much later—maybe around age seventy. So the risks are delayed.

So as men live longer and longer, would you expect to see their osteoporosis risk approaching that of women?

Yes. One of the reasons that so many men don't suffer from osteoporosis is that they die before women. I believe average life expectancy for American men is about seventy-three or seventy-four—it's seventy-seven in Japan—but even among women the most severe forms of osteoporosis occur after age seventy—around seventy-five. So, men don't have the same

opportunity to suffer from osteoporosis. That is one reason. The other is the slow start of osteoporosis in males.

Why is osteoporosis called the Silent Killer?

Osteoporosis doesn't provoke any noticeable symptoms in the beginning—not for some years. Only when the bone actually breaks or deforms and the osteoporosis is advanced does it become apparent. To diagnose osteoporosis at an earlier stage requires measurement of bone mass, and bone mass measurement has not been available until very recently. So we don't know when osteoporosis is becoming a problem. So that's why we call it a 'silent; disease. We call it a 'killer' because it is by no means harmless. It is as terrible a killer as myocardial infarctions or strokes. The only difference is that osteoporosis for a woman or for a man progresses more slowly than a myocardial infarction. It takes years to provoke a hip fracture, for example. The hip is the largest bone in the body. Bone density diminishes over many years and patients gradually experience difficulty rising and walking. Confinement to bed is very common. Then they develop thrombosis, pneumonia—all these diseases which cause them to slowly die. That's why we call it the Silent Killer, or the Silent Epidemic.

What is the role and importance of calcium in the human body?

Calcium is the fifth largest component of the human body after carbon, hydrogen, nitrogen and oxygen, the constituents of organic compounds. It is the most abundant mineral in the body. That makes it very important. Ninety-nine percent of calcium is in the bone, but the remaining one percent is distributed throughout the cells. In each cell and of course in blood there's always some calcium, and this calcium outside the bone is even more important than the calcium that's giving strength to the bone. All cells—hormone secreting cells, heart cells, liver cells, kidney cells and brain cells—need calcium to perform their functions. That's why calcium is vital to human beings.

You've been conducting research on a special form of calcium. Can you tell us about it? Not all calcium preparations are alike. Some are more easily absorbed than others. Generally speaking, calcium is one of the least absorbable compounds. For example: sugar. If you eat something sweet, almost 100% is absorbed immediately, including vitamins and other materials. But only 20% or so of the calcium you eat is absorbed. This is a very, very low figure—only onefifth of what we eat! So we have to improve the absorption of calcium in order to really help the body to utilize calcium. We have had a recent breakthrough in the form of AAACa (U.S. brand name is AdvaCAL), which is quite absorbable, unlike all other calcium preparations. We make this by heating oyster shell in a vacuum, then adding some similarly treated algae to this. We call it HAI—Heated Algal Ingredient and this combination of oyster-shell calcium and Algal Ingredient makes it very absorbable—much better than any other calcium preparation so far.

What are the greatest advantages of AAACa (AdvaCAL) over supplements like calcium citrate or calcium carbonate?

Well, some preparations are better than others. Calcium citrate is one of the better ones. Calcium carbonate is most commonly used but the body's absorption of calcium carbonate is very poor, unless we have very strong stomach acid. That is why we recommend the use of calcium carbonate when you eat. Calcium contained in your food or taken with food is usually better absorbed than most calcium supplements alone. That's because the gastric acid is released in response to the food. But AAACa is so readily soluble in water that it doesn't even need gastric acid. Anybody can take it. Unless it is readily soluble in water, of course, it doesn't get into the blood. So one advantage of AAACa is high *solubility*. The second advantage is its high *availability* prompted by the algal ingredient.

Tell us about your research on osteoporosis and bone mineral density as affected by AAACa versus other calcium supplements.

To show whether AAACa is really effective against osteoporosis we have to perform bone measurement. Now any studies which are not randomized or placebo-controlled are not considered valid these days, so I did all these procedures with a group of very elderly ladies-in their eighties. These ladies were deficient in calcium and calcium absorption. If we could demonstrate an effect in these ladies it would no doubt help others to have better absorption. So the challenge-the most difficult part first-was to choose a placebo that contains no calcium. but which looks exactly like the calcium preparation so that these people didn't actually know which was calcium and which wasn't. Even the doctors were blind to the nature of the drug. That's what we call a double-blind procedure. Neither the doctor nor the patient knows which is which. And we used calcium carbonate too, for a total of three groups-AAACa, calcium carbonate and placebo-for two years. It took quite a long time and some of these patients dropped out for various reasons. But a good number continued for the full twenty-four months and we found a very impressive increase in bone-mineral density (BMD) in those who received AAACa and a very significant fall of BMD in those who took placebo. Everybody is getting older and losing bone, so we expect such a loss. So even if we are able to merely sustain the BMD, that would be very interesting, but there was a significant increase in BMD for AAACa users. This was quite surprising. In fact, no other existing preparation has been able to produce a definite increase in BMD. Calcium carbonate, by the way, just about sustains BMD and is maybe slightly better than placebo, but can't compare with AAACa.

That clinical study was done with elderly patients—a very tough population. Have you studied pre-menopausal women?

Yes. We have studied middle aged women—around fifty to sixty. There are several ways to measure BMD. Some of them are more sensitive than others, so for this study on the middle-aged we have chosen the best and most sensitive measurement available—Peripheral Computer Tomography. This method is characterized by separate measurements for cortical (hard) and trabecular (spongy) bone. This spongy bone is more sensitive to the increase of calcium or other drugs because they have a more abundant blood supply, and are more elastic and changeable. By measuring spongy bone of the forearms we demonstrated a 3% increase of BMD. This was after only four months. It's really amazing because no other method or preparation, calcium or otherwise, has ever demonstrated a significant increase in bone mineral density in just four months.

You mean even drugs like calcitonin and hormones were unable to perform like that? I don't believe so, no. So I was quite excited when I saw these results. The study is all written up but remains to be published.

How did you dose these patients in your study?

In all these studies we selected 900mg of elemental calcium a day for both AAACa and calcium carbonate.

You have developed a theory which you call the 'Calcium Paradox.' What exactly does it say?

It's a paradox because we see the opposite of what we would expect. All of us are calcium deficient. I think everybody agrees with that. Everybody also agrees that when we are deficient in blood calcium, the bone will lose its calcium. Whole body calcium deficiency runs parallel to bone calcium deficiency. Calcium deficiency is a cause of osteoporosis, though others may cite other causes—for example estrogen deficiency also contributes to calcium deficiency. We summarize by saying the cause of osteoporosis is calcium deficiency. But the paradoxical part occurs when the parathyroid hormone secretion increases in response to the blood calcium deficiency. The first important thing about calcium is that we should have an abundant supply to keep our bones strong. The next most important is its function in heart and brain action, and

interview with dr. takuo fujita, m.d.

Exhibit 7

Page 3

muscles. All these vital body functions are maintained by a constant abundance of calcium in the body. If we don't keep calcium levels in the blood constant, the heart stops. Dr Ringer of England demonstrated this many years ago and we still use Ringer's calcium solutions. If you add calcium chloride to a saline (sodium chloride) solution, the heart will beat. Dr Ringer demonstrated this with a frog's heart. He removed the heart, put it in saline solution and the heart stopped. When he added calcium to the solution, the heart began to move. The fact that we need a constant amount of calcium is the beginning of the calcium paradox theory. We must keep our blood calcium constant but we don't eat enough calcium. If this calcium deficiency were to bring down blood calcium, your heart would stop. That's a terrible thing. Fortunately, it doesn't stop because in response to even a very slight fall of blood calcium, the parathyroid hormone takes calcium out of the bone. Compared with the modest needs of the rest of the body, bone is an almost endless supply of calcium. It's like a bank with a large amount of money. If you have a problem, you go to the bank and borrow. The parathyroid hormone is like a cash card. But if you use your cash card enough times, your bank account will become exhausted. That's osteoporosis. And now the paradox begins. Calcium coming out of the bone enters other tissues where there shouldn't be any calcium to begin with. For example, in the blood vessels. Blood vessels should be soft and elastic. Bones should be hard and strong. There shouldn't be too much calcium in the blood vessels. They become hardened. We call this arteriosclerosis, and blood pressure rises. This is the first calcium paradox disease which came to our attention. Deficiency of calcium results in flooding of calcium in the blood vessels. The second calcium paradox disease is perhaps Alzheimer's disease. If calcium levels rise in the brain cells, brain function starts to decline, you start forgetting things and finally you don't know who you are or anything. This is caused by an increase of calcium in the brain cells. Again, this results paradoxically from calcium deficiency. The parathyroid hormone takes calcium out of the bone and puts it in the brain cells. We don't want them to do this but this is one of the unfortunate byproducts of calcium deficiency. There are many other calcium paradox diseases, for example osteoarthritis is a degeneration of cartilage and loss of calcium to bring bone-onbone in scraping contact in the joints. The formation of osteophytes-bone outgrowths-slowly leads to pain, but the increase of calcium in the cartilage is the first event. Loss of calcium from bone leads to increase of calcium in cartilage. There are many other examples, like diabetes mellitus, some cancers---colon cancer is already established to be caused by calcium deficiency. Calcium enters the cell, the cell starts to proliferate, divide and subdivide until it becomes cancerous. So calcium deficiency is the root of all evil and the cause of many diseases associated with aging. This is the calcium paradox.

So you're saying that the parathyroid gland removes calcium from the bones at such a rate that our health is compromised?

Our body should be very wise. It shouldn't make any mistakes. But in this instance I don't know. Sometimes, it does strange things. Why does the parathyroid hormone take an excessive amount of calcium? Because there is so much calcium in the bones—ten thousand times more than we eat or have in our blood or soft tissue, so even our wise body doesn't exactly do the best thing. That is one thing I don't understand. But we have all the facts and the calcium paradox is only one attempt to explain all these facts. I don't really have an answer.

All your studies so far have been done in Japan, but some people may be concerned that the Japanese diet is different from the North American diet. Would you expect to see similar results in a North American study group?

Well, the Japanese live very long. They have the highest longevity in the world. They say that fish and seaweed is good for them. The sushi bar is quite popular in this country. But the only trouble with the Japanese diet is that it is very low in calcium content. You are taking more calcium here in this country and in the Western world than in Japan. Other countries in Asia like Korea and China also have very low calcium intake, so that may be one reason why calcium is so effective in Japan. But I think we can expect similar effects—maybe not the same but similar—in the United States, because many investigators in the United States also point out

interview with dr. takuo fujita, m.d.

that even Americans are not taking enough calcium. In addition to the intake of calcium we have also to think of the loss of calcium. If you take large amounts of protein or phosphates—if you eat meat and all kinds of delicious foods you're already taking a lot of phosphates and protein and that will accelerate the loss of calcium in the urine. So we have to consider both sides what you are taking and what you are losing. I'm afraid that although Americans are taking more calcium, they're also losing more calcium. So I think we are almost equal. We are taking less calcium, but our calcium loss may also be lower, so I'd expect similar effects.

It's important to note that you were giving your patients about 600mg of calcium a day with food. According to U.S. figures I've read, that's about what the typical American receives.

That's right. Actually calcium intake varies widely among different countries. Some people take enough calcium—mainly health-conscious people—but elderly people in most countries are not taking enough. Their appetite diminishes and they don't feel right. And of course the problem of sunshine exposure is very important. Without sufficient exposure to sunlight, you can't make enough Vitamin D to stimulate calcium absorption. Some people in the United States are also calcium deficient, like many Japanese, and I don't think there's too much difference in calcium intake.

In the United States, a calcium and magnesium complex is quite popular. How would you compare that compound with AAACa (AdvaCAL)?

Well, calcium and magnesium are both important but we don't have to combine them. The ratio of calcium to magnesium is not important, as long as we are taking enough of both. Too much calcium intake is never dangerous, but too much magnesium can be. So I think calcium is the only one of which you can take as much as you want and get away with it, but you shouldn't take too much magnesium. I don't think we have to combine these two. You may take magnesium if it's necessary. Too much calcium may constipate you—it's one of the unavoidable effects of calcium because calcium takes water away from food and makes the stool harder. Magnesium doesn't do that, so that's why magnesium is used against constipation. I already use magnesium along with calcium, but not as a fixed preparation.

AAACa is comprised of calcium hydroxide and calcium oxide, which you have mentioned are highly soluble in water. Can their high solubility produce any side effects or other problems?

Strangely, I encountered no side effects except maybe some constipation in some people. You may feel a little full in your stomach if you take a large amount of calcium but it doesn't mean that calcium decreases the appetite. Hyper-acidic people—who secrete more acid in the stomach—may tend to have ulcers, and calcium neutralizes gastric acid. But when calcium disappears from the stomach there may be a rebound of gastric acid secretion. It doesn't happen in healthy people, only hyper-acidic people have this problem.

You've done some interesting research on calcium and fat reduction. Please describe it. In this group of elderly ladies—the first group we studied—I didn't really expect the effects we saw. We were measuring the whole body—bone, fat and muscle—and in addition to the increase in BMD I found a definite decrease in the fat content of the body. I was at first skeptical because I didn't expect this effect. But it's there. In the placebo-controlled subjects there was a slight increase of fat but among the others there was a definite decrease from 23% to 18% fat. Body weight didn't change that much, so it means that AAACa was able to get rid of some of the fat.

Please comment on the incidence of fractures among AAACa users.

Of course, any increase in BMD promises fewer fractures and for women in their eighties, there was no increase in fractures while they were on AAACa, but out of the thirty-placebo-controlled subjects there were three fractures. This number is not large enough but it suggests that

LL770

interview with dr. takuo fujita, m.d. Page 5

new york, june 16, 1999

AdvaCAL prevents decrease of bone strength. So it's quite possible that AdvaCAL would prevent fractures.

If the parathyroid gland is clever enough to extract calcium from bone when it's necessary, why doesn't it regulate the amount it selects? That's a very good question, but I don't really have an answer.

Are other factors involved, or is this purely the responsibility of the parathyroid?

The parathyroid is a very strange hormone. To begin with, there is no parathyroid in fish, but they live easily without it. They are continually inhaling calcium-rich water and have a non-stop supply of calcium. It only develops in creatures living on land, like ourselves. There might be some difference between constant increase in parathyroid hormone and occasional (periodic) increase. Now, is parathyroid hormone good or bad? It must be good because we need parathyroid hormone. But constantly high parathyroid hormone levels are not good. We have statistics showing that people with lower parathyroid hormone live longer and those with higher parathyroid hormone levels die earlier. They don't live long at all.

Do they die of any particular illness?

Oh, cancer, even osteoporosis. The best thing is, we should have an optimum amount of parathyroid hormone and in general we need lower levels. But sometimes we need elevated parathyroid hormone levels.

Would you describe the parathyroid function as an emergency mechanism?

Yes. It helps us out in an emergency but it would be better if it weren't necessary. We have a group of patients with renal insufficiency—those undergoing dialysis. There we know the parathyroid hormone is very important because if we lose our kidney function, then we can't make active vitamin E. These patients with kidney failure always show a greater calcium deficiency than healthy people and parathyroid hormone levels are always higher. The parathyroid hormone has been identified as one of the toxins leading to uremia—loss of kidney function. So this mistake may occur when the hormone is acting as a toxin, or perhaps there's an excessive amount of hormone in the blood. Optimum parathyroid hormone levels are harmless and don't bring calcium into the soft tissue of the blood vessels, heart or the brain. So the problem may be one of excessive parathyroid hormone secretion. There's no clear answer, I must confess.

Why is no vitamin D added to AAACa (AdvaCAL)?

Because HAI acts like vitamin D. AAACa was very effective in the group of elderly ladies we studied. They were deficient in vitamin D because they were hospitalized, and even though the sunshine passes through the windows, there are no ultra-violet rays. So most people in hospital become vitamin D deficient. Also, older patients are always deficient in vitamin D. In spite of this AAACa was very effective. We don't need vitamin D because HAI performs the same function. And it's a natural product.

Is it possible that vitamin D is more helpful when taken with some calcium preparations than with others?

Yes. It all depends on the solubility of the product in question. It must be soluble and iodized. Otherwise it just goes through the gut. According to some figure, it is more soluble than others, even calcitonin—five to ten times more soluble. Solubility is very easy to measure by electrical conductivity. Soluble ions conduct electrical current. AAACa is amazingly soluble.

What is the effect of exercise on osteoporosis?

Exercise will activate the bone cells to prevent calcium loss from bone. And if you stop exercise, the reverse process occurs. You lose bone. So by exercising, you are preventing bone loss. Both exercise and calcium intake are important—we can't substitute exercise for calcium. But if

interview with dr. takuo fujita, m.d.

new york, june 16, 1999

Page 6

we exercise more, we also stimulate calcium absorption. It increases appetite, so you eat more, and an elevated metabolism stimulates calcium absorption. So all these things aid calcium absorption.

Is weight-bearing exercise more useful?

Yes. It is physical pressure on bone that stimulates bone cells. But all exercise, weight-bearing or not, stimulates calcium absorption. Swimming, for example, is non weight-bearing. Walking is weight-bearing. Calcium absorption is also affected by emotional factors. Exercise is good relaxation that makes you feel happier and stronger. This is important because you have to be happy. You have to be out of distress to absorb enough calcium. Stress and unhappiness decrease calcium absorption. Adrenaline and cortico-steroid hormones are secreted during stress. They facilitate calcium loss and prevent gut absorption. You can eat a lot of calcium, but if it's taken in a state of harmony, while chatting with friends, for example, then more calcium is absorbed. So what we need are three things: calcium, exercise and happiness. And of course calcium makes you happy. So calcium is everything!

What about dietary sources of calcium?

Milk is a very common source of calcium, but it also contains a lot of phosphorus, which combines with calcium and prevents it from being absorbed. Tofu is good, but not many North Americans eat it. You can eat small fish with bones, like sardines—even canned sardines. But bone calcium is also rich in phosphorus. The ideal dietary source should be low in phosphorus and high in calcium. For Americans milk is alright. It is readily absorbed. They say that broccoli and kale are better than milk, but they don't contain much calcium and you have to eat such large quantities that it's not practical. In general, milk is alright. If you are high in cholesterol then low-fat milk is all right. But I would recommend AAACa over any dietary source, because it has no phosphorus. It's superior to any calcium found in foods.

What about people who are not suffering from serious osteoporosis but just want to prevent it. We don't want to tell everybody to go on calcium therapy...or do we? Oh sure—*everybody* should take calcium. I'm not osteoporotic, but I take it regularly. As a result my EKG went down. Another thing—calcium makes you happy. It works against stress. In Japan we have a very popular TV program called Pocket Monster. It's for kids. Six hundred kids went into convulsions, attacks, seizure because of this show. They got so excited they stopped breathing, then they started to hyperventilate. Calcium has a tranquilizing effect. So kids watching television should take calcium first. It keeps you happy and peaceful. That's why everybody needs calcium and you don't have to be osteoporotic to take it.

So perhaps we could use calcium to promote world peace.

Well, it's strange. You may find me overenthusiastic about calcium, but as the years go by I have no reason to reverse myself, because I don't find anything against it. All the facts go along with my theory.

The only thing against it is constipation?

Not against it, but we expect it. America has a stressful society like Japan and we you calcium to make you less stressful, so there will be less crime and less juvenile delinquency and all these things. You need calcium in the schools.

What is the physiological basis for happiness?

Any minor decrease in blood ionized calcium will make you unhappy. The brain or muscles become excited when there's even a slight fall in blood calcium levels, especially ionized calcium. There are two types of calcium—protein-bound and ionized. Although we're talking about ionized calcium, we just say calcium. If there is a slight decrease in calcium then you are more excited and irritable. A readily absorbable calcium will correct the slight decrease of blood calcium promptly. A slight decrease of blood calcium makes everybody uneasy and irritable. I

interview with dr. takuo fujita, m.d.

see a good example in Alzheimer's patients, who become irritable towards the evening. We call it the Sundowning Syndrome. As the sun goes down, they become excited and they suffer from various complexes. For example, a persecution complex makes them see anyone who approaches them as having bad intentions. Even Alzheimer's patients staying at home may be afraid to go out because the world seems a dangerous place. That's why we keep Alzheimer's patients in a closed room and sometimes have to lock the room-otherwise if they go out, especially in the evening, it could be dangerous. They could be hit by a car. But we can prevent sundown syndrome in Alzheimer's patients by giving them calcium in the afternoon. They become quieter. There's a very slight decrease of blood calcium towards evening. Perhaps healthy people experience a slight decrease too, but it's not noticeable, but in Alzheimer's patients it is noticeable. I have already published this study on convulsions in children watching TV. We tried some experiments. We didn't want to produce convulsions in children, so we took teenagers, 18 to 20 year-old students. We gave them some money and they watched TV. They were happy to cooperate. They didn't suffer convulsions but their blood calcium levels declined while watching the show-an action story with an exciting soundtrack. One day we measured their blood calcium. It came up low. The next day, we gave them AAACa two hours before watching the same show. Then, their blood calcium remained constant. They don't feel anything because the drop was minor, but we clearly demonstrated the effect of supplementing calcium. We had to use ionized calcium so that it could be directly measured. This requires special apparatus. I wrote a paper on the subject.

As opposed to protein-bound?

Yes, because calcium is associated with protein very easily, according to stress or other conditions. The ionized fraction act directly on the brain, and protein acts as a kind of buffer. Usually, we measure total calcium, which doesn't change very easily, but if we measure ionized calcium we can show these effects. Calcium is a kind of hormone, in the same way as vitamin D. Simple minerals like potassium, sodium and all other salts don't have receptors. Receptors are very important. Receptionists in offices who screen everybody coming in are like hormonal receptors. Calcium has a receptor, too. No other mineral have receptors. We call it a calcium *sensor*, or calcium *receptor*. It is a treatment for VIPs. Not like ordinary minerals. Some people may think calcium's dangerous because we call it a hormone, but that's not the case. We think of it as *like* a hormone—as *important* as a hormone, as *specific* as hormones to accomplish certain functions. So calcium is very special.

Does it fit the definition of a hormone or are you using this as an analogy? All hormones have receptors. Calcium is the only mineral with receptors. So we can say that calcium is a unique mineral that is like a hormone. Let's call it the happy hormone!

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to treat, cure or prevent any disease. Exercise and a healthy diet with adequate daily calcium intakes may help younger white and Asian women reduce their Osteoporosis risk in later life. Calcium intakes above 2,000 mg are not likely to provide extra benefit.

INTRODUCTION

Lane Laboratories (the Sponsor) markets a calcium supplement preparation, developed and supplied by Fujix, Inc., of Japan. The source is of uncertain composition, but is based on heat-treated oyster shells, to which a small quantity of an algal extract is added. Lane Laboratories had provisional bioavailability data supplied by Fujix, but was desirous of determining if the supplier's results could be duplicated by a disinterested third party. Accordingly, Lane Laboratories approached the Osteoporosis Research Center of Creighton University to conduct suitable bioavailability tests, comparing the Lane product ("AdvaCal") with another popular calcium supplement ("Citracal" – Mission Pharmaceutical, San Antonio, Tx).

1

METHODS

Subjects. Subjects were 24 healthy postmenopausal women, average age 58.5 (\pm 5.2) yrs. 13 were receiving ERT/HRT and continued throughout the study, and 11 took no HRT. Subjects who habitually had used calcium supplements were asked to abstain beginning 5–7 days prior to beginning the comparative study of AdvaCal and Citracal. In order to ensure similarity of vitamin D status, all subjects were given 25(OH)D [Calderol®], 20 µg every other day, starting 5–7 days prior to the first test day and continuing for the duration of the study. Pertinent personal information is listed in Table 1 at the end of this report.

All subjects gave signed consent and the project was approved by the Creighton University Institutional Review Board. A copy of the consent form is included in the Appendix, along with copies of other pertinent forms used in the project.

Investigational Design. The design of the study was a randomized cross-over, comparing absorbability within subject. The hypothesis underlying the project was that AdvaCal would be absorbed more efficiently than calcium citrate (in the form of Citracal), and the corresponding null hypothesis was that there was no difference in absorbability between the two products. Each subject was assigned a sequence of "ca" or "ac", where "c" stands for Citracal and "a" for AdvaCal. The sequences were assigned to the subjects in the order of entry, using the random number function of Excel (Microsoft Corporation, Redmond, WA).

Protocol. After screening and obtaining consent, subjects reported to the ORC in the morning, fasting. A blood sample was taken to establish the baseline serum calcium value. Then the subjects were fed a standard light breakfast consisting of two pieces of Center-baked, Italian style, low calcium white bread, toasted, with one pat of butter for each, plus a cup of coffee or tea (without cream or whitener) but with artificial sweetener if desired. Midway during breakfast the subjects swallowed the test products and the time was noted. Then blood samples were drawn at 1, 3, 5, 7, and 9 hours thereafter for measurement of total serum calcium. Lunch was provided in the hospital, but subjects subjects resumed their usual routine (except continuing to abstain from calcium supplements where applicable) and returned approximately one week later for the second test in the sequence, when the above routine was repeated. The average interstudy interval was 7.5 days.

Analyses. Serum calcium was analyzed by atomic absorption spectrophotometry (AAnalyst 100, Perkin-Elmer, Norwalk, CT). Both calcium products were dissolved in hydrochloric acid and their calcium content analyzed also by atomic absorption.

Test Products. The two test products were Advacal, supplied by Lane Laboratories (Lot No. 6369; Expiration date 7/03), and Citracal (Lot No. OC55; Expiration date 3/02). Six capsules, each labeled to contain 150 mg and analyzed to contain an average of 166.4 mg calcium, constituted the test dose of AdvaCal, and three tablets, labeled to contain 315 mg and analyzed to contain 318.3 mg each, constituted the test dose of Citracal. Thus, the aggregate dose for AdvaCal was 998.4 mg, and for Citracal, 954.9 mg.

The AdvaCal product was further analyzed to determine its homogeneity and calcium density. The standard deviation of the weight of a batch of 15 capsules was 2.17%, and the calcium content of the powder within the capsule was 40.7% by weight, close to the theoretical value, but very slightly above the level which we typically find for laboratory-synthesized, precipitated calcium carbonate.

Statistical Analysis. The primary outcome variable was the area under the curve for the increment in serum calcium above baseline, from 0 to 9 hours (i.e., AUC₉), calculated by the trapezoidal method. Statistical significance was tested by repeated measures ANOVA, testing for treatment and order. Pharmacokinetic parameters were estimated using an exponential model and a 0.75 hour time delay between ingestion and absorption, employing PK Analyst (MicroMath, Salt Lake City, UT).

RESULTS

The principal results of the study are contained in Table 2, which sets forth, for each subject, the serum calcium value at each sampling point for each product, together with the respective AUC_9 values and the within-subject difference between products. Fig. 1 presents the aggregated data by product, first for total serum calcium (A) and then for the increment above baseline induced by the absorbed calcium (B).

AUC₉ for AdvaCal averaged 3.148 ± 0.307 (SEM) and for Citracal, 4.386 ± 0.394 (SEM). AUC₉ varied within subject, reflecting the usual day-to-day variability in absorptive performance. AUC₉ was higher for Citracal than for AdvaCal in 17 of the 24 subjects, and higher for AdvaCal in 7. The mean within-subject difference between the paired values for AUC₉ (AdvaCal minus Citracal) was -1.238 ± 0.385 (SEM). This Citracal was 0.804 ± 0.088 (SEM).

Pharmacokinetic estimation of AUC_{∞} , using the data available out to nine hours postingestion, yielded an estimate of 4.10 for AdvaCal and 6.18 for Citracal. Cmax was 0.567 and 0.712 mg/dl for the increment in serum calcium for the two products, and Tmax was 3.32 and 3.86 hours, respectively.

4

DISCUSSION

For products that cannot be labeled with a suitable isotopic tracer, the pharmacokinetic method used in this investigation, i.e., comparing the small rise in serum calcium induced by the absorption of calcium from two or more test products; constitutes the preferred approach to evaluating bioavailability. Absolute absorbability is not available with this method; instead reference is made to another, established product – in this case Citracal. The roughly 20% lower absorbability of the two sources (as judged from the mean AUC₉ ratio) could theoretically mean that calcium citrate was more efficiently absorbed than calcium carbonate. However, that has shown not to be true in a variety of other studies (1-3). In a randomized cross-over design comparing intrinsically labeled calcium citrate with calcium carbonate (1), our group found, if anything, slightly better absorbability for the carbonate salt. Sheikh et al. (2), using the intestinal wash-out method, also found somewhat greater absorbability for the carbonate than for the citrate.

An additional possibility would be that the pharmaceutical formulation altered the intrinsic absorbability of the calcium salt contained in a particular marketed product. Work in our laboratory has confirmed that formulation can be an important determinant of bioavailability. However, in a project just completed in our laboratory, and submitted for publication (3), we compared, using methods essentially the same as those employed in this project, one of the leading marketed calcium carbonate products, with one of the leading marketed calcium carbonate products, with one of the two.

Thus, we conclude that there was something about the AdvaCal product which rendered its calcium slightly less absorbable than that of calcium citrate (and by extension, of other calcium carbonate products, as well, which have, as noted, been shown to be identical to calcium citrate). At the same time it must be said that, while absorbability for AdvaCal is not as good as had been hoped, certainly not superior to that of at least one currently marketed product, it still can be a useful calcium source. If the ratio of the absorbability of the two products is calculated as the simple arithmetic mean of the within-subject ratios, the resulting value (0.804) narrowly falls within the range for bioequivalence defined by the FDA (i.e., 0.80 to 1.25). However, if the ratio is calculated as the geometric mean, as the FDA may require (4), then the ratio falls below 0.80.

Page 5.

REFERENCES

- 1. Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. *Osteoporosis Int* 9:19-23, 1999.
- 2. Sheikh MS, Fordtran JS. Calcium bioavailability from two calcium carbonate preparations. *N Engl J Med* 323:921, 1990.
- 3. Heaney RP, Dowell, MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr (submitted) 2000.
- 4. Center for Drug Evaluation and Research, Food and Drug Administration, US Dept of Health and Human Services. Statistical procedures for bioequivalence studies using a standard two-treatment crossover design, 1992. http://www.fda.gov/cder/guidance/index/htm

Reports\Lane Lab AdvaCal

		Medications			blood pressure RX;multivits;Vit E;ca (stopped for study)	ped during study)		Prinivil'Timoptic/Xalatan;Aleve;ASA; multivits (stopped for stu		Vit C & E; lutein				Vit C & E; Ca (stopped during study); Flonase rarely	•		Vits E & C,folic acid, stopped Ca & multivits for study	Slucosamine; Chondroitin		Synthroid;Claritin;Flonase (occ);Vits C,E;ca (stopp	t; Lotensin;Aspirin;Vision Formula			multivits,Vit E; occas.Ca (stopped during study)	Brewer's Yeast' Vit a. Ca (stonned during outs)	s, og (supper duingstugy)	r usalilax, gli iko, ca(stopped during study)			
			Paxil;Lipitor		blood pressure RX	multivits & ca (stopped during study)		Prinivil'Timoptic/X ₈	Vioxx; multivits	multivits (stopped);Vit C & E; lutein	Claritin-D;ASA daily			Vit C & E; Ca (stop			Vits E & C, folic acid	Synthroid;Feldene;(Synthroid; Claritin; Fl	Zocor;Elavil;Sineme			multivits;Vit E; occa	Brewer's Yeast Vit	Energy of June 1997	rusaiilax, yiiiko; ua			
Table 1. Pertinent personal characteristics of study subjects		-0.70/00 GM		LMP 10 yrs. Ago; EKT last 2 years	LMP 16 yrs ago; started ERT 2 yrs ago	LMP 8 yrs ago; ERT				•	nyster @ 35yo;BSO @ 42yo; ERT ever since	LMP mid 805;ERT first 3 yrs; then quit	hyster only @ 32yo; no ERT at all	nyster in '84; ERT since '98	LMP U//80; no ERT	nyster age 29; EKI since age 50;quit spring 2000			LIMIP 0-/ yrs. ago;started ERT 3 yrs ago	LMP 9 yrs ago; ERT last 10-11 yrs.	nyster age 30; menop late 40s; ERT last 4-5 yrs Zocor; Elavii; Sinemet; Lotensin; Aspirin; Vision Formula	nyster in '86; ERT off & on first few yrs; then none	LMP @ 45 yo;ERT 3 mo. in Lilly Study	for one year	LMP '88; no ERT	ERT ever since				
of stu	Smoker		3	⊒	2	2	2				<u>s</u>	yes	2	2	8 9	S :	UII		2	2	lottier	2	2,	former	2	former				
stics o	Interstudy 2nd interval (d)			- 1	- 6	ų r		~ ^		- ~				~ ~				- ~						9	9	7	7.50	2.89		
acteri	2nd	9/16/00	10/14/00	10/0/01	10/2/00		0/22/00	0/20/00	10/9/00	10/7/00	10/0/00	10/0/01	10/11/00	10/16/00	10/16/00	11/14/00	11/6/00	11/R/00	11/11/00	11/18/00		00/07/14		00/12/11	00/17/11	11/18/00				
char	, 1	00/6/6	10/7/00 1										-			• `			~			•			-	11/11/00 11/			•	
sonal	Wť	70.1	82.6	·						67.4 9					66.5 1(-			÷						/4.9 11/1	76.1	9.96		
ant per	Ht (m)	1.576	1.588	1.643	1.628	1.632	1.598	1.661	1.566	1.629	1.675	1.719	1.522															0.069		
ertine	Age	53.0	53.6	66.4	61.5	58.8	59.5	60.8	60.4	57.2	65.1	59.2	56.4	64.3	58.6	61.1	52.7	48.4	46.2	57.7	65.6	55.5	61.1	64.4		0.00	58.5	5.2		
ц. 1. Г.	Seq	Š	AC	AC	CA	AC	AC	AC	G	CA	СA	Ч	AC	AC	сA	ĊA			AC	S		SA								
Lage	٩	ACal01	ACal02	ACal03	ACal04	ACal05	· ACal06	ACal07	ACal08	ACal09	ACal10	ACal11	, ACal12	ACal13	ACal14	ACal15	ACal16	ACal17	ACal18	ACal19	ACal20	ACal21	ACal22	ACal23	ACaP4		Mean	xhi n s	ibit 8	3

Pag

LL1221

		Time (hrs)								163	
		Subst	0	1	3	5	7	9	AUC	a-a	
ACal										-3.75	
Visit 1	S Ca	С	9.45	9.85	5 10.67	' 10.64	10.31	10.07	92.81		0.516
	Incr S Ca	t i	0.00	0.40					7.76		
Visit 2	S Ca	a	9.46	9.57					1		
	Incr S Ca		0.00								
ACal	02		،						• •		
Visit 1	S Ca	a	8.84	9.05	0.50					2.135	1.527
	Incr S Ca		0.00	9.05 0.21			9.72				
Visit 2	S Ca	Ċ	9.27				0.88		6.185	ĩ	
	Incr S Ca	,		9.45		9.89	9.64	9.77	87.480)	
		. 1	0.00	0.18	, 0.65	0.62	0.37	0.50	4.050)	
ACall	13									0.445	
Visit 1	SCa.	a	9.67	9.40	<i>9.81</i>	10.19	9.85	9.80	88.435	-0.445	0.759
	Incr S Ca		0.00	-0.27	0.14	0.52		0.13			
Visit 2	S Ca	c	9.64	9.34	9.72	10.27	9.97	9.86	1.405		
	Incr S Ca	·	0.00	-0.30	0:08	0.63	0. <i>33</i>	0.22	88.610 1:850		
ACal0	d			,				1			
Visit 1	S Ca	c	9.20	0.74	10.00					-4.245	0.414
	Incr S Ca		9.20 0.00	9.74	10.28	10.31	9.99	9.67	90.040		
Visit 2	S Ca	a	9.31	0.54	1.08	1.11	0.79	0.47	7.240		•
	Incr S Ca		0.00	9.56 0.25	10.19	9.49	9.53	9.37	86.785		
		1	0.00	0.25	0.88	0.18	0.22	0.06	2.995		•
ACal05								•		0.290	1.099
Visit 1	S Ca	a	<i>9.71</i>	9.74	10.28	1.0.24	10.13	9.83	90.595	0.290	1.099
	Incr S Ca		0.00	0.03	0.57	0.53	0.42	0.12	3.205		
Visit 2	S Ca	c	9.36	9.39	9.89	9.77	9.72	9.63	87.155		
•	Incr S Ca		0.00	0.03	0.53	0.41	0.36	0.27	2.915	. •	
ACal06				,				•			
Visit 1	S Ca	a	9.76	9.56	10.00	10.08	0.70	. محما		-3.165	0.236
			0.00	-0.20	0.33	0.32	<i>9.78</i>	9.70	88.820		•
Visit 2	S Ca	c	9.61	9.5 <u>6</u>	 10.33	0.52 10.41	0.02	-0.06	0.980		
	Incr S Ca		0.00	-0.05	0.72	0.80	10.08	9.85	90.635		
	•	I	0.00	0.05	0.72	0.00	0.47	0.24	4.145		
ACal07										0.910	0.710
Visit 1	S Ca	a	9. <u>5</u> 5	9.33	9.78	10.09	9.87	9.71	87.960	-0.810	0.713
	Incr S Ca		0.00	-0.22	0.23	0.54.	0.32	0.16			
Visit 2	S Ca	c	9.61	9.71		10.13	9.95	1	2.010		
	Incr S Ca		0.00	0.10	0.29	0.52	9.95. 0.34		89.310		
		I			0.27	0.52	0.34	0.37	2.820		

Table 2. Serum calcium following ingestion of calcium sources

Exhibit 8 **LL1222**

		Time (hrs)									
•		Subst	0	1	3	5	7	9	AUC9	a–c	a/c
ACal08				<u>.</u>		·····				-1.695	
Visit 1	S Ca	С	9.10	9.26	9.77	9.86	9.92	9.74	87.280		0.005
	Incr S Ca		0.00	0.16	0.67	0.76		0.64	5.380		
Visit 2	S Ca	а	9.21	<i>9.18</i>	9.91	9.86	-	9.44	86.575		
	Incr S Ca		. 0.00	-0.03	0.70	0.65	0.40	0.23	3.685		
ACal09			*							0.010	1 00 0
Visit 1	S Ca	c	9.37	9.51	10.03	9.83	9.69	9.48	07 520	0.912	1.285
	Incr S Ca		0.00	0.14	0.66	0.46	0.32		87.530		
Visit 2	S Ca	a	9.26	9.195	9.94	10.09	9.66	0.11	3.200		
	Incr S Ca		0.00	-0.06	0.68	0.83	9.00 0.40	9.65 0.39	87.453 4.113		
ACal10										-2.840	0.014
Visit 1	S Ca	c	9.84	9.82	10.48	10.41	10.01	9.99	91.440	-2.040	0.014
	Incr S Ca		0.00	-0.02	0.64	0.57	0.17	0.15	2.880		
Visit 2	S Ca	a	10.07	10.17	10.41	10.12	9.83	9.66	90.670		
	Incr S Ca	.	0.00	0.10	0.34	0.05	-0.24	-0.41	0.040		
ACal11							. •			-1.780	0.606
Visit 1	S Ca	c	9.61	9.59	9.94	10.59	10.25	10.26	91.010	1.700	0.000
•	Incr S Ca		0.00	-0.02	0.33	0.98	0.64	0.65	4.520		
Visit 2	S Ca	a	<i>9.85</i>	<i>9.85</i>	10.19	10.66	10.01	9.97	91.390		
	Incr S Ca		0.00	0.00	0.34	0.81	0.16	0.12	2.740		
ACal12										-0.250	0.937
Visit 1	S Ca	a	9.41	9.53	10.34	10.1	9.68	9.14	88.380	0.200	0.237
	Incr S Ca		0.00	0.12	0.93	0.69	0.27	-0.27	3.690		
Visit 2	S Ca	C	<i>9.15</i>	9.25	9.62	9.96	9.65	9.38	86.290		
	Incr S Ca		0.00	0.10	0.47	0.81	0.50	0.23	3.940		
ACal13										-0.705	0.818
Visit 1	S Ca	a	9.82	9.86	10.24	10.36	10.33	9.98	91.540	0.705	0.010
	Incr S Ca		0.00	0.04	0.42	0.54	0.51	0.16	3.160		•
Visit 2	S Ca	c	· <i>9.83</i>	<i>9.7</i> 8	10.57	10.58	10.28	9.89	92.335		
	Incr S Ca	ļ	0.00	-0.05	0.74	0.75	0.45	0.06	3.865		
ACal14	· .		•							-1.335	0.834
Visit 1	S Ca	c ·	9.20	9.52	10.59	10.51	10.06	9.63	90.830 [.]		.0.04
	Incr S Ca		0.00	0.32	1.39	1.31	0.86	0.43	8.030		
Visit 2	S Ca	a	9.12	9.47		10.21	9.65		8.050 88.775		
	Incr S Ca		0.00	0.35	1.35	1.09	9.03 0.53	0.23	6. <i>695</i>		
								-			

Table 2. Serum calcium following ingestion of calcium sources

Page 9

LLE1223 8

		·			Time	(hrs)			50470		
		Subst	0	1	3	5	7	9	AUC9	<i>a–c</i>	a/c
ACal15	,									0.495	1.361
Visit 1	S Ca	С	9.50	9.66	9.67	<i>9.</i> 80	9.59	9.51	86.870		
	Incr S Ca	1	0.00	0.16	0.17	0.30	0.09	0.01	1.370		
Visit 2	S Ca	a	9.41	9.4	10.13	9.7	<i>9.35</i>	9.39	86.555		
•	Incr S Ca	r	0.00	-0.01	0.72	0.29	-0.06	-0.02	1.865		
ACal16			۲							2 00	
Visit 1	S Ca	c	9.40	9.52	10.23	10.81	10.63	10.30	92.620	-3.90	0.514
	Incr S Ca		0.00	0.12	0.83	1.4 <u>1</u>	1.23	0.90	92.020 8.020		
Visit 2	S Ca	a	9.22	9.1	9.87	10.03	1.25 9.65	9.74	87.100		
	Incr S Ca		0.00	-0.12	0.65	0.81	9.03 0.43	0.52	4.120		
		1						1			
ACal17										-2.195	0.601
Visit 1	S Ca	a	9.10	9.26	9.73	9.37 [.]	9.65	9.27	85.210		
	Incr S Ca	:	0.00	0.16	0.63	0.27	0.55	0.17	3.310		
Visit 2	S Ca	c	9.38	9.69	10.17	10.14	10.09	9.9	<i>89.925</i>		
	Incr S Ca		0.00	0.31	0.79	0.76	0.71	0.52	5.505		
ACal18										1.650	1.728
Visit 1	S Ca	a	9.35	9.54	9.77	10.14	9.85	9.56	88.065	1.050	1.720
	Incr S Ca		0.00	0.19	0.42	0.79	0.50	0.21	3.915		
Visit 2	S Ca	с	9.47	<i>9.5</i> 8	9.85	9.8	9.72	9.65	87.495		
	Incr S Ca		0.00	0.11	0.38	0.33	0.25	0.18	2.265		
ACal19											
Visit I	S Ca		0 70	0.0	11.02	10.00				-4.340	0.268
1 1016 1	Incr S Ca	C	9.78 0.00	9.8	11.03	10.75	10.33	10.14	93.950		
Visit 2	S Ca	a	0.00 9.69	· 0.02	1.25	0.97	0.55	0.36	5.930		
r wa 2	Incr S Ca	u	9.09 0.00	9.57 -0.12	10.07	10.04	9.79		88.800		
		i I	0.00	-0.12	<i>0.38</i>	0.35	0.10	0.11	1.590 ·		
ACal20	·	•								1.010	1.277
Visit 1	S Ca	с <u>–</u>	9.38	<i>9.2</i> 8	10.05	10.38	9.60	9.40	88.070		e en
	Incr S Ca		0.00	-0.10	0.67	1.00	0.22	0.02	3.650		
Visit 2	S Ca	a	9.37	9.29	10.28	10.34	<i>9.79</i>	9.55	88.990		
	Incr S Ca		0.00	-0.08	0.91	0.97	0.42	0.18	4.660·		
ACal21										0.540	1.040
Visit 1	S Ca	c	9.54	9.75	10.1	9.78	9.72	9.46	99 NEE	0.540	1.246
	Incr S Ca	-	0.00	0.21	0.56	9.78 0.24	9.72 0.18		88.055		
Visit 2	S Ca	a	9.66	9.75	10.13	0.24 10.19	0.18 9.91	-0.08	2.195 80.675		
	Incr S Ca	-	0.00	0.09	0.47	0.53		9.76	89.675		
	LINE D'OU	I	0.00	0.09	U.4/	0.00	0.25	0.10	2.735		•

Table 2. Serum calcium following ingestion of calcium sources

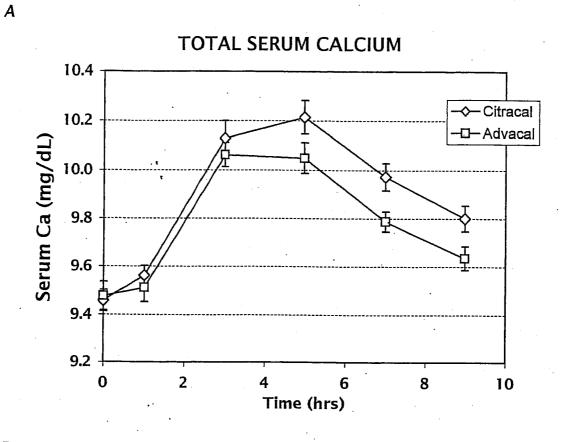
Page 10

Exhibit 8 LL1224

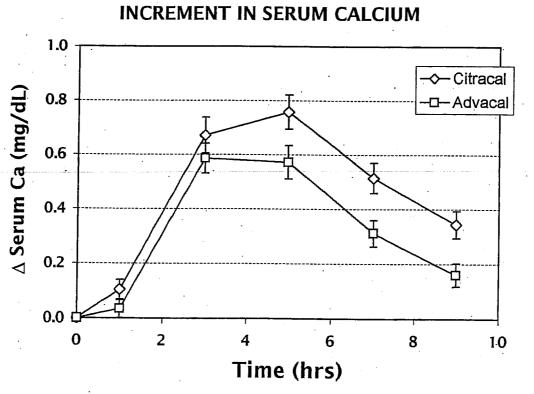
					Time	(hrs)		i			
		Subst	0	1	3	5	7	9	AUC9	a–c	a/c
ACal22								•		-2.050	0.518
Visit 1	S Ca	a	9,59	9.78	9.99	9.87	9.74	9.85	88.515		
	Incr S Ca	۱	0.00	0.19	0.40	0.28	0.15	0.26	2.205		
Visit 2	S Ca	С	9.47	9.48	10	10.29	10.04	9.87	<i>89.4</i> 85		
	Incr S Ca	۲ I	, 0.00	0.01	0.53	0.82	0.57	0.40	4.255		
ACal23			r	· •						-0.830	0.803
Visit 1	S Ca	a	9.73	9.84	10.45	10.18	10.00	10.07	90.955		
	Incr S Ca	r I	0.00	0.11	0.72	0.45	0.27	0.34	3.385		
Visit 2	S Ca	C	9.65	9.76	10.23	10.31	10.23	10.06	91.065		
	Incr S Ca		0.00	0.11	0.58	0.66	0.58	0.41	4.215		
ACal24								·		-2.405	0.543
Visit 1	S Ca	c	9.18	9.20	10.05	9.95	9.87	9.75	87.880		
	Incr S Ca		0.00	0.02	0.87	0.77	0.69	0.57	5.260		
Visit 2	S Ca	a	<i>9.28</i>	9.25	<i>9.93</i>	9.47	9.75	9.56	86.375		
	- Incr S Ca	:	0.00	-0.03	0.65	0.19	0.47	0.28	2.855		

Table 2. Serum calcium following ingestion of calcium sources

Mean	-1.238	0.804
StDev	1.888	0.430
N	24	24
SEM	0.385	0.088
t	-3.213	



B



Page 12

Original Research

Absorbability and Cost Effectiveness in Calcium Supplementation

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Key words: calcium absorption, calcium carbonate, calcium citrate, bioavailability, cost-effectiveness

Background: Cost-effectiveness of calcium supplementation depends not only on the cost of the product but on the efficiency of its absorption. Published cost-benefit analyses assume equal bioavailability for all calcium sources. Some published studies have suggested that there are differences in both the bioavailability and cost of the major calcium supplements.

Design: Randomized four period, three-way cross-over comparing single doses of off-the-shelf commercial calcium supplements containing either calcium carbonate or calcium citrate compared with a no-load blank and with encapsulated calcium carbonate devoid of other ingredients; subjects rendered fully vitamin D-replete with 10 μ g/day 25(OH)D by mouth, starting one week prior to the first test.

Subjects: 24 postmenopausal women

Methods: Pharmacokinetic analysis of the increment in serum total and ionized calcium and the decrement in serum iPTH induced by an oral calcium load, based upon multiple blood samples over a 24-hour period; measurement of the rise in urine calcium excretion. Data analyzed by repeated measures ANOVA. Cost calculations based on average retail prices of marketed products used in this study from April through October, 2000.

Results: All three calcium sources (marketed calcium carbonate, encapsulated calcium carbonate and marketed calcium citrate) produced identical 24-hour time courses for the increment in total serum calcium. Thus, these were equally absorbed and had equivalent bioavailability. Urine calcium rose slightly more with the citrate than with the carbonate preparations, but the difference was not significant. Serum iPTH showed the expected depression accompanying the rise in serum calcium, and there were no significant differences between products.

Conclusion: Given the equivalent bioavuilability of the two marketed products, the cost benefit analysis favors the less expensive carbonate product.

INTRODUCTION

There is general acceptance of the importance of achieving adequate calcium intakes throughout life, and in most adults effort in that regard means taking some form of calcium supplement. Over half the women enrolled in the Women's Health Initiative reported using supplements, and that figure rose to nearly 60% in women over age 70 [1]. While calcium supplementation has generally been considered a cost effective intervention [2,4], much depends upon the cost of the preparation. Thus Torgerson and Kanis, in the UK, calculated that calcium was not cost effective for a preparation they priced at \sim \$0.50/g in current dollars [5]. Lowering that cost modestly produced a more favorable relationship. Bendich *et al.* [4] found that calcium supplementation at 1200 mg/day and a cost of \$0.10-0.12/g was cost effective for all US women 75 years of age or older when calculated against the costs of care associated only with hip fracture. If the endpoint was increase in bone mineral density and its associated lower total fracture risk, then calcium supplementation was cost effective even with universal supplementation of all US men and women 65 years of age or older. An additional consideration, given virtually no attention to

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date, involves factoring in bioavailability of the calcium source. Most, if not all, analyses to date have assumed equivalent bioavailability for different salts and different consumer formulations. Recent publications by Heller *et al.* [6,7] suggested that this might not be the case. The authors reported absorbability for a calcium citrate supplement superior to that of a commercially marketed calcium carbonate product. Since the two salts, in pure form, had been shown in several studies to be absorbed equally well [8–10], a question arose as to whether differences in pharmaceutical preparation of marketed products might have interfered with or enhanced the absorbability of one or the other preparation. Such absorptive effects, if they exist, would alter cost effectiveness calculations, once calcium *actually delivered* into the blood stream becomes the basis for the computation.

Accordingly we set out to compare two commercial supplements, using standard pharmacokinetic methods, both with one another and with non-pharmaceutical calcium carbonate ingested without excipients. This communication describes the results of this investigation. Additionally, we then used the bioavailability data to calculate the costs associated with providing the two commercially available calcium salts to the US population at greatest risk of hip fracture.

MATERIALS AND METHODS

Subjects

Subjects were 24 postmenopausal women aged 56.1 \pm 7.1 years and in good general health. Their BMI was 29.3 \pm 5.2 kg/m². Thirteen subjects were receiving estrogen replacement therapy, and the remaining 11 were not. One was African-American; the others were Caucasian. Subjects taking calcium supplements were asked to abstain throughout the course of the study, starting at least one week in advance of the first test. Additionally, subjects were counseled by our research dietitian to hold calcium from dietary sources to under 400 mg/day. mainly by avoiding all dairy products. Also, they were instructed to avoid high sodium foods (such as commercial fast foods and canned soups or soup mixes) starting two days prior to and including each test day. To eliminate any variability in absorptive performance due to vitamin D insufficiency or to seasonal change in vitamin D status, all subjects were given 10 μ g 25(OH)D₃ (Calderol®, Organon, West Orange, NJ)/day starting one week before the first test and continuing throughout the study. This dose is approximately equivalent to 1000 IU (25 μ g) of cholecalciferol, but produces a rapid elevation of serum 25(OH)D, in contrast with the five month time-to-equilibrium required when using cholecalciferol. Further, this dose is the amount required, at Omaha's latitude, to bring serum 25(OH)D concentration up to 32 ng/mL (80 nmol/L), a level widely considered to be the lower limit of physiological normal. The study was approved by the Creighton University

240

Institutional Review Board, and each subject gave written consent.

Design

The study was a four-period, three-way randomized crossover, within-subject design, with each individual receiving Os-Cal® (a product manufactured by GlaxoSmithKline and consisting of calcium carbonate derived from oyster shell), Citracal® (a product manufactured by Mission Pharmacal and consisting of calcium citrate), a gelatin capsule containing precipitated calcium carbonate or an empty gelatin capsule (the blank). The test source was ingested midway through a standard light breakfast containing two pieces of Italian-style white bread (Center-baked from unenriched flour), toasted and buttered, together with a cup of coffee, tea or water (with artificial sweetener if desired), plus additional water to ensure adequate urine volume. Blood samples were taken at 0, 1, 3, 5, 7, 9, 12, and 24 hours for measurement of total and ionized calcium and parathyroid hormone (PTH). Urine was collected in two pools, from 0 to 5 hours, and from 5 to 24 hours, and was analyzed for calcium, creatinine and sodium. Calcium sources were given only on the test day and only at the breakfast meal. The noon meal was provided by Center staff between the 5 and 7 hour blood draws and was designed to be low in both calcium and sodium. The evening meal was ingested between the 9 and 12 hour blood draws. Tests were separated typically by seven days; in this way the entire suite of studies was completed for most subjects within a 22-day period so as to minimize temporal variability in absorptive performance.

Test Sources

For the two commercial products (Os-Cal® and Citracal®), the sources were purchased from a retail pharmacy. The labeled content of elemental calcium for the Os-Cal® was 500 mg, plus 200 I.U. of vitamin D (Control No. 9K2228; exp. date 11/01). In order to approximate the load size of the Os-Cal®, the Citracal® dose required a combination of two different formulations, one labeled to contain 200 mg elemental calcium (Lot 9D12; exp. date 4/02) and the other 315 mg plus 200 I.U. vitamin D (Lot 9E86; exp. date 5/01). Precipitated calcium carbonate was prepared in the Center's laboratory by dissolving reagent grade calcium chloride in distilled water, heating to 80°C with stirring and adding a slight stoichiometric excess of a heated aqueous solution of sodium carbonate, timed so that the reaction was completed within one minute. The resulting precipitate was collected on a fritted glass filter, washed with deionized water to remove adsorbed sodium chloride, dried at 90°C overnight, ground in a mortar and packed loosely into tared gelatin capsules in sufficient quantity to provide a 500 mg calcium load per dose. All preparations were chemically analyzed; actual ingested loads of calcium were as follows: for Os-Cal®, 503 mg; for Citracal®, 516 mg, and for precipitated calcium carbonate, 497 mg.

VOL. 20, NO. 3

Analytical Methods

Calcium in serum, urine and the ingested sources was analyzed by atomic absorption spectrophotometry (AAnalyst 100, Perkin-Elmer, Norwalk, CT), creatinine in urine by an auto analyzer method (Chiron Express Plus, Ciba Corning Diagnostics, Medfield, MA) and sodium in urine by an ion selective electrode method (Cobas Integra, Roche Diagnostics, Basel, Switzerland). Serum ionized calcium was analyzed under standardized test conditions by an ion selective electrode method (Nova Nucleus, Nova Biomedical, Waltham, MA). Serum immunoreactive parathyroid hormone (iPTH) was measured as the intact molecule by IRMA (Nichols, San Juan Capistrano, CA).

Data Handling and Statistical Analysis

The primary outcome measures were the usual pharmacokinetic variables, area under the curve (AUC), both at five hours and at 24 hours (for both total and ionized serum calcium), as well as the time of maximum serum concentration (Tmax) and the magnitude of the elevation (Cmax). AUC was calculated by the trapezoidal method, and Cmax and Tmax were analyzed both by taking the observed values for concentration and time and by fitting the means of the timed serum increments for each source, using a first-order, two-compartment model with an absorptive delay of 0.5 hours (PKAnadyst; Micro-Math Scientific Software, Salt Lake City, Utah). The curves were plotted, and the pharmacokinetic parameters were calculated, both as the absolute values and as the increment above baseline. Secondary variables were serum iPTH and urine calcium, the latter with and without adjustment for urine sodium. AUC for iPTH was calculated using the same approach as for serum calcium. The sodium adjustment was made in two ways, using a slope factor of either 0.004 mg Ca/mEq sodium or 0.010 mg Ca/mEq Na. In each case adjustment was to the mean sodium excretion value for a given calcium source. The first factor is in the middle of the range reported in the literature for the relationship of urine calcium and sodium [11,12]. The second factor was derived from the slope of urine calcium to urine sodium observed with the blank meal in the subjects of this investigation. For the test calcium sources, urine calcium values are reported as the increment above the calcium content of the corresponding collections obtained on the test day with the blank load,

A standard bioequivalence analysis [13] was performed both on serum total and serum ionized calcium, using AUC from 0 to 5 and 0 to 24 hours, as well as Cmax and Tmax. AUC for serum PTH was also compared. Only the data from the first three periods were used in these bioequivalence analyses, since the treatment in the fourth period (non-pharmaceutical calcium carbonate) was not in random order. A general linear model was fit with the natural logarithm of the variate as the dependent variable, test source, sequence, period and subject nested

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

in sequence as factors and the pre-dose value of the parameter as a covariate. The test sources in this equivalence analysis were Os-Cal®, Citracal® and blank. The sequence (or order) effect was tested using the subject in sequence mean square as the error term. The adjusted mean difference between the carbonate and citrate sources was computed and its 90% and 99% confidence intervals were constructed. The difference and the bounds of the confidence interval were exponentiated to obtain the ratio of the carbonate source mean to the citrate source mean and its confidence interval. As set forth in the applicable FDA Guidelines [13], if the confidence interval for the ratio fell in the range from 0.80 to 1.25, bioequivalence was considered to have been demonstrated.

Cmax and Tmax were compared between treatment groups using paired t tests. Pharmacokinetic parameters for Os-Cal® and Citracal® were each compared to blank using linear contrasts in the general linear model described above. Pharmacokinetic parameters for Os-Cal® and Citracal® were each compared to CaCO3 using paired t tests. Changes from pre-dose serum concentrations of total and ionized calcium were compared among treatment groups at each time point using doublyrepeated measures ANOVA. Each pairwise comparison among test sources was tested and type I error was controlled at the 5% level using Holm's step-down method. Urine calcium and sodium-adjusted urine calcium were compared between calcium sources using paired t tests. AUC values for incremental calcium and PTH ratio to baseline were correlated by standard Pearsonian regression. All of these analyses used within-subject differences to make inferences concerning the pharmacokinetic parameters, and in this way full adjustment was made for between-subject differences in absorptive efficiency.

To determine the cost of these supplements, we used the average price at all US outlets and also calculated separately the mass market costs/g of elemental calcium for Os-Cal \otimes and for Citracal \otimes between April and September 30, 2000. The data are provided by AC Nielson. The savings associated with hip fracture reduction were based on a previous analysis of this issue [4] for calcium supplements generally, which in turn used the average 1995 cost per discharged patient with a hip fracture, the size of the age cohort concerned and the fractional reduction in risk derived from published trials of calcium supplementation.

RESULTS

Table 1 presents the pharmacokinetic parameters for both total and ionized serum calcium for the four test sources, and Fig. 1 and 2 show the time courses of total and ionized calcium, respectively. The AUC values for the three calcium sources were all highly significantly different from the blank (p < 0.001), but there was no significant difference between the three calcium-containing sources for either of the AUC values

Parameter	$\begin{array}{l} \text{Os-Cal} \\ n = 24 \end{array}$	Citracal $n \leftarrow 24$	$CaCO_3$ n = 23	Blank
Total Ca			n 23	<u>n = 24</u>
Increment AUC ₅ Increment AUC ₂₄ Cmax Tmax Ionized Ca	$\begin{array}{c} 1.81 \pm 0.22 \\ 6.69 \pm 1.07 \\ 10.3 \pm 0.07 \\ 4.8 \pm 0.51 \end{array}$	$\begin{array}{c} 1.88 \pm 0.18 \\ 5.91 \pm 1.02 \\ 10.3 \pm 0.08 \\ 4.2 \pm 0.36 \end{array}$	$\begin{array}{c} 1.95 \pm 0.15 \\ 6.39 \pm 0.85 \\ 10.3 \pm 0.07 \\ 4.1 \pm 0.32 \end{array}$	$\begin{array}{c} 0.04 \pm 0.14 \\ -0.05 \pm 0.77 \\ - \end{array}$
Increment AUC ₅ Increment AUC ₂₄ Cmax Tmax measured in mg/dL · hour, Cma:	$\begin{array}{c} 0.83 \pm 0.11 \\ 2.36 \pm 0.56 \\ 5.3 \pm 0.02 \\ 5.1 \pm 0.91 \end{array}$	$\begin{array}{c} 1.02 \pm 0.11 \\ 3.58 \pm 0.53 \\ 5.4 \pm 0.03 \\ 4.3 \pm 0.43 \end{array}$	$\begin{array}{c} 0.85 \pm 0.10 \\ 2.58 \pm 0.46 \\ 5.3 \pm 0.03 \\ 3.1 \pm 0.26 \end{array}$	-0.05 ± 0.09 0.47 ± 0.56

Table 1. Serum Calcium Pharmacokinetic Parameters (Mean ± SEM)

in mg/dL, Tmax is measured in mg/dL, Tmax is measured in hours.

or any of the other pharmacokinetic parameters. Also, as Fig. 1 shows graphically, the three sources produced virtually identical total serum calcium time courses, whether expressed as absolute values (Fig. 1A) or as increment above baseline (Fig. 1B). Serum calcium values differed significantly from the corresponding values following the blank load at all time points from 3 to 12 hours for Os-Cal® and from 1 to 9 hours for Citracal®, but there were no significant differences between the calcium sources at any time point. Fig. 2B shows that the incremental elevation of serum ionized calcium for the citrate source was somewhat greater from 5 to 12 hours compared to Os-Cal® and from 5 to 9 hours compared to the plain calcium carbonate. Consistent with this difference, the AUC24 for ionized calcium (Table 1) was greater for the citrate than for the carbonate preparations. However, given the dispersion of the individual AUC data, none of these differences was statistically significant. There was no effect of the order of the test substance on any of the outcome variables. Similarly, age and estrogen status were also tested and were without effect on the relative absorbabilities of the test calcium sources.

Standard bioequivalence analysis of AUC and Cmax indicated that the carbonate and citrate test sources were bioequivalent with respect to serum total and ionized calcium (Table 2). In fact, for all parameters, the ratio of the values for the two sources differed from unity by less than 1%. Both the carbonate and citrate test sources were significantly different from blank: with respect to AUC and Cmax for serum total and ionized calcium. There was no evidence of a difference between the Os-Cal® and CaCO₃ or between Citracal® and CaCO₃ with respect to AUC, Cmax, or Tmax for serum total and ionized calcium, with one partial exception. The time to peak concentration was approximately one hour later with the Citracal® test source than with the CaCO₃ test source (p < 0.05) when using the measured data. Using the mean data fitted to a pharmacokinetic model (a probably better approach), no significant differences were found between the Tmax estimates for any of the sources.

Fig. 3 presents the scrum iPTH values for all four sources, first as absolute values (A), then as fractions of the baseline value (B). As is evident, depressions for the three calcium sources were virtually identical, amounting to a drop of $\sim 40\%$ at three hours after calcium ingestion. The AUC₂₄ values for iPTH (not shown) did not differ among the calcium sources, but all three sources did differ significantly from the blank. For both of the carbonate sources (data not shown), but not for the citrate, AUC₂₄ for the iPTH decrement from baseline was significantly correlated with AUC₂₄ for incremental [Ca²⁺] (p < 0.001).

Table 3 presents the urine calcium increments for the three calcium-containing sources above the corresponding urine calcium excretion values for the blank load. Both from 0 to 5 hours and from 5 to 24 hours, the urine calcium increments differed significantly from zero for all three sources. The citrate produced a $\sim 40\%$ greater rise in urine calcium from 5 to 24 hours than either of the carbonate preparations, but, given the wide dispersion of individual values, the difference between sources was not significant. Calcium and sodium excretion were significantly correlated in our subjects as expected (data not shown), and both methods of correcting for sodium excretion slightly reduced the dispersion of the urine calcium values, like the uncorrected, did not differ significantly between calcium sources.

The costs of the two supplements and cost:benefit analyses are presented in Table 4. Columns 4 and 8 contain the net benefit of supplementation (in dollars per capita for the population treated). A positive value means that the savings exceed the cost, while a negative value means a net cost. (A negative value is not necessarily bad, since prevention of most diseases usually carries a net cost. Thus the principal value of the net benefit figure is to facilitate comparison between sources.) The citrate source we tested costs between 1.5 and 1.8 times as much as the carbonate source, per gram of elemental calcium. Provision of the carbonate product to all US women 75 years of age and older for 2.83 years was projected to be cost effective,

VOL. 20, NO. 3

242

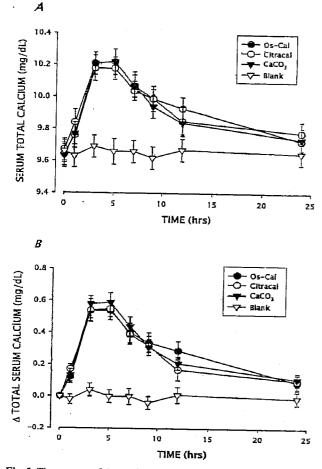


Fig. 1. Time course of the total serum calcium, both as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

saving \$100 million in hip-fracture associated, costs/year; by contrast, the citrate source was not cost effective. If increasedbone mineral density is assumed to be predictive of hip fracture reduction, then universal supplementation of all men and women aged 65 years and older remains cost effective using the

Table 2. Bioequivalence Analysis

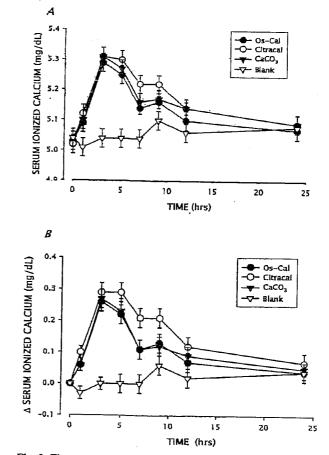


Fig. 2. Time course of the ionized serum calcium increment above baseline for the three calcium sources and for the blank load, both as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

carbonate as the calcium source; the net potential benefit is \$478 million/year or a per capita benefit of \$14.26. It is worth noting that the annual cost for providing 1000 mg of elemental calcium as the carbonate preparation is less than \$70 per person.

Ratio: Os-Cal to Citracal	90% CI	99% CI	Conclusion*
0.999	0.990, 1.007	0.095 1.017	
1.004	•	•	bioequivalent
1.003	•		bioequivalent
0.994	•		bioequivalent
0.992	•	•	bioequivalent
0.995			bioequivalent bioequivalent
-	Os-Cal to Citracal 0.999 1.004 1.003 0.994 0.992	Os-Cal to Citracal 90% CI 0.999 0.990, 1.007 1.004 0.995, 1.012 1.003 0.991, 1.014 0.994 0.985, 1.002 0.992 0.986, 0.998	Os-Cal to Citracal 90% CI 99% CI 0.999 0.990, 1.007 0.985, 1.013 1.004 0.995, 1.012 0.990, 1.018 1.003 0.991, 1.014 0.984, 1.021 0.994 0.985, 1.002 0.980, 1.008 0.992 0.986, 0.998 0.982, 1.002

* Bioequivalence is concluded if the 90% confidence interval falls between 0.80 and 1.25. The analysis was performed on log-transformed data, and the difference between adjusted means for Os-Cal and Citracal was exponentiated for the ratio. The upper and lower confidence bounds on the difference between the adjusted means were exponentiated for the upper and lower bounds on the ratio presented in the table.

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

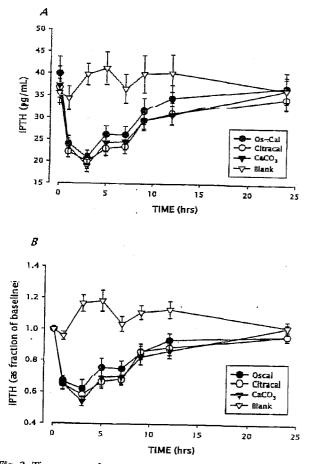


Fig. 3. Time course of serum iPTH following ingestion of the three calcium sources and for the blank load, both as absolute values (A) and as fractional values relative to baseline (B). Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000, Used with permission.)

DISCUSSION

Calcium supplementation has been shown, in well-controlled clinical studies, to slow age-related bone loss and reduce the risk of hip and other fractures in middle aged and older men and women. Using U.S. data on the medical costs associated with hip fracture compared to the costs of preventive supplementation with calcium, Bendich *et al.* found that supplementation targeted at those at greatest risk could save over \$2.5 billion/year [4]. However, cost-effectiveness of calcium supplementation depends not only on the cost of the product, but on the efficiency of its absorption. All published cost-benefit analyses to date have assumed not only an average price per gram of calcium regardless of the salt, but equal bioavailability for all calcium sources.

Shangraw [14] had previously shown marked differences in dissolution of calcium supplement preparations, due solely to pharmaceutical formulation differences, and unpublished experience of one of us (RPH) has demonstrated that not all preparations of the same salt exhibit equivalent absorbability. Finally, Heller et al. [7] explicitly raised this question in their recent paper. It is reassuring, therefore, to note that, in this study, Os-Cal® and the non-pharmaceutic, precipitated calcium carbonate exhibited identical bioavailability values. Thus for at least one marketed calcium carbonate product, pharmaceutical formulation does not alter the intrinsic bioavailability of its calcium sait. The same conclusion is probably applicable to the marketed citrate product as well. This is because it did not differ from non-pharmaceutic calcium carbonate in this study and because we had previously shown that the bioavailability values of the pure carbonate and citrate salts were identical [8].

Interestingly, however, and not previously described, several small differences were noted in pattern of response between the citrate and carbonate sources. None was statistically significant in isolation, but taken together, their mutual consistency suggests underlying differences in metabolic response to the two salts. These effects were i) although the rise in total calcium was the same, slightly less of the increment in serum calcium following the carbonate products was carried as the ionized form and slightly more as the bound form, relative to the citrate salt; ii) PTH suppression was slightly greater for the Citracal® than for the Os-Cal®, and the difference approximately coincided with the time points at which the ionized calcium differences were most prominent; and iii) urine calcium excretion in the 5 to 24 hour pool was higher for the Citracal® than for Os-Cal®. The relative depression is shown most clearly in Fig. 4, which plots ionized calcium as a percent of total calcium and shows slightly lower values for the Os-Cal® from 5 to 9 hours. This relative depression may reflect a very slight degree of alkalosis due to exhalation of CO_2 from the carbonate anion, but the reason for the delay after ingestion

Table 3. Urine Calcium Increments after Ingestion of Test Calcium Source	*29
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		0-5 hours			5-24 hours		0-24 hours		
	N	Меац	SEM	N	Mean	SEM		Mean	051
Os-Cal	23	21	3	22			11	Ivican	SEM
Citracal	23	16	2		22	8	22	43	10
CaCO ³	21		3	22	30	10	22	46	9
- C1	41	20	4	20	20	10	20	38	0

* mg Ca above the corresponding excretion following the blank load.

244

VOL. 20, NO.

Table 4. Cost: Benefit Analysis of Two Calcium Supplements

		Mic	u and women (n = 33	1 aged < 03 ,540,000)	years	Women aged ≥ 75 years (n = 9,426,000)			
Os-Cal 500 mg Ca + 200 IU D	No. of tabs per bottle	Cost per person 1 year (\$) (1)	Cost for 1 year (\$ million) (2)	Net benefit (\$ million) (3)	Net per-capita benefit (\$) (4)	Cost per person 2.83 year (\$) (5)	Cost for 2.83 year	Net benefit (\$ million) (7)	
Os-Cal 500 mg Ca + 200 IU D Citracal 200 mg Ca Citracal 200 mg Ca Citracal 315 mg Ca + 200 IU D Citracal 315 mg Ca + 200 IU D Citracal 315 mg Ca + 200 IU D	75 160 200 100 60 120	68.62 58.54 86.69 116.25 123.02 92.02	2,302 1,963 2,907 3,899 4,126 3,086	140 478 466 1,457 1,684 645	4.18 14.26 13.89 43.45 50.22 19.22	194.20 165.67 245.34 329.01 348.16 260.44	1,831 1,562 2,313 3,101 3,282 2,455	-169 100 -651 -1439 -1620 -793	(8) -17.88 10.65 -69.02 -152.69 -171.84

(1) Mass market costs (AC Nielsen) for one year's supply for one person at 1,000 mg elemental calcium per day. (2) Cost for one year's supply for this population (N \times (1)).

(3) Preventable total expenditures (\$2,442 million for 1995 in this population) minus the cost of supplying the entire population for one year (2). (4) Not benefit divided by the population size ((3) \div N).

(5) Mass market costs (AC Nielson) for 2.83 years' supply for one person at 1,000 mg elemental calcium per day. (6) Cost for 2.83 years' supply for this population (N \times (5)).

(7) Preventable total expenditures (\$1,662 million for 1995 in this population) minus the cost of supplying the entire population for 2.83 years (6).

NB: Calculations based on Tables VI, VII. From: Supplemental Calcium for the Prevention of Hip Fracture: Potential Health-Economic Benefits [4]. PapsBKB_Cost Ca

is unclear. Physiologically, these changes are mutually consistent, since a higher ionized calcium would be expected to lead to a greater depression of PTH release, to an increased filtered calcium load at the kidney and, through lowered PTH, to decreased tubular reabsorption of calcium. Although the greater rise in urine calcium with calcium citrate was not statistically significant in this study, it is worth noting that Heller et al. [7] reported a significant loss of calcium in urine following supplementation with calcium citrate (Citracal®) which was not seen with an equivalent dose of calcium carbonate (Os-Cal®).

We had not designed the study to evaluate this issue, and, indeed, we had not anticipated it. Nevertheless, it is worth noting that the finding of a slight increase in calcium excretion with the citrate source is consistent with what we had reported previously [8]. In that earlier investigation, despite identical tracer-based absorption fractions for the citrate and carbonate salts of calcium, there was a tendency for the urine calcium increment to be greater with the citrate than with the carbonate. We had attributed that finding to a calciuric effect of absorbed citrate, but, in view of the ionized calcium findings in this study, it may, instead, reflect a mild alkalotic effect of the carbonate salt.

On a methodologic note, it may be worth mentioning that the increments in urine calcium were substantially more variable than the increments in serum calcium. The coefficients of variation (CVs) of the serum and urine calcium increments at their peak values (3 and 5 hours for serum and 0 to 5 hours for urine), for all calcium sources, were 38% to 60% for serum and 77% to 99% for urine. This roughly twofold greater variability underscores, as we have noted previously [8], the relative

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

weakness of using the rise in urine calcium to estimate absorptive performance, particularly for loads as small as 500 mg.

For this study, the retail cost per 1000 mg of ingested calcium was between \$0.16 and \$0.20 for the marketed calcium carbonate product and between \$0.24 and \$0.38 for the marketed calcium citrate product. Since both sources exhibited equivalent bioavailability, it is clear that the carbonate source was the less expensive of the two per unit of absorbed calcium and would therefore exhibit a more favorable cost-benefit relationship in a cost-effectiveness analyses such as set forth in Table 4. Additionally, although not usually considered in cost benefit analysis, the greater calcium density of carbonate-based

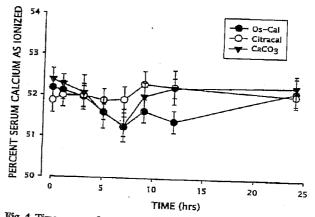


Fig. 4. Time course of serum ionized calcium expressed as a percent of total serum calcium for the three calcium sources. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

245

products means that fewer pills are needed to achieve a desired supplement intake, a factor known to influence patient compliance [15].

In this study we used 25(OH)D as a rapid and efficient means of ensuring approximately equivalent vitamin D status in all subjects. Such treatment would not be a part of population-level supplementation, and its costs are, accordingly, not a part of our calculations. Vitamin D is contained in both of the supplements tested here, and its cost is, therefore, already factored into the analysis summarized in Table 4.

While we tested only two commercially available products in this analysis, our purpose was not so much to contrast these two specifically as to use them as examples for a type of calculation and analysis that should be performed for all marketed calcium supplement products. It was beyond the scope of this project to undertake an exhaustive survey of different pharmaceutical formulations, although we believe this should be done. It is a matter of commonplace experience that there are many other calcium products available, at least some of which explicitly meet the USP disintegration and dissolution standards for calcium supplements (and therefore can be presumed to have a bioavailability comparable to what we found here). Their prices range from as low as \$0.09 per 1000 mg to as much as \$0.53. Lacking bioavailability data for most of these products, it is uncertain whether any of them would exhibit an advantage over the products tested here.

In conclusion, based upon bioavailability, cost and clinical efficacy, calcium carbonate, in the form of Os-Cal®, would appear to be a good choice for calcium supplementation in a US population at risk for both low bone mineral density and hip fracture.

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REFERENCES

1. Jackson RD, LaCroix A, Cauley J, McGowan J: WHI calcium and vitamin D triel baseline monograph. Annels Epidemiel (submitted) 2000.

- Chrischilies EA: Public health implications of interventious to promote calcium intake: cost-benefit considerations. Paper presented to the NIH Consensus Development Conference on Optimal Calcium Intake, June 1994, Washington, DC.
- Eddy DM, Johnson Jr CC, Cummings SR, Dawson-Hughes B, Lindsay R, Melton III LJ, Slemenda CW: Osteoporosis: Review of the evidence for prevention, diagnosis and treatment and costeffectiveness analysis. Osteoporos Int 8(Suppl 4):S1-S88, 1998.
- Bendich A, Leader S, Muhuri P: Supplemental calcium for the prevention of hip fracture: potential health-economic benefits. Clin Ther 21:1058-1072, 1999.
- Torgerson DJ, Kanis JA: Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. Q J Med 88:135-139, 1995.
- Heller HJ, Stewart A, Haynes S, Pak CYC: Pharmacokinetics of calcium absorption from two commercial calcium supplements. J Clin Pharmacol 39:1151–1154, 1999.
- Heller HJ, Greer LG, Haynes SD, Poindexter JR, Pak CYC: Pharmacokinetic and pharmacodynamic comparison of two calcium supplements in postmenopansal women. J Clin Pharmacol 40:1237-1244, 2000.
- Heaney RP, Dowell MS, Barger-Lux MJ: Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 9:19-23, 1999.
- Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS: Gastrointestinal absorption of calcium from milk and calcium salts. N Engl J Med 317:532-536, 1987.
- Recker RR: Calcium absorption and achlorhydria. N Engl J Med 313:70-73, 1985.
- Itoh R, Suyama Y: Sodium excretion in relation to calcium and hydroxyproline excretion in a healthy Japanese population. Am J Clin Nutr 63:735-740, 1996.
- Nordin BEC, Need AG, Morris HA, Horowitz M: The nature and significance of the relationship between urinary sodium and urinary calcium in women. J Nutr 123:1615-1622, 1993.
- 13. Center for Drug Evaluation and Research, Food and Drug Administration, US Dept of Health and Human Services: Statistical procedures for bioequivalence studies using a standard twotreatment crossover design, 1992. http://www.fda.gov/cder/ guidance/index/htm
- Shangraw RF: Factors to consider in the selection of a calcium supplement. In "Proceedings of the 1987 Special Topic Conference on Osteoporosis." Public Health Rep S104:46-49, 1989.
- Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR: The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 150:1881-1884, 1990.

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Original Research

Absorbability and Cost Effectiveness in Calcium Supplementation

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Key words: calcium absorption, calcium carbonate, calcium citrate, bioavailability, cost-effectiveness

Background: Cost-effectiveness of calcium supplementation depends not only on the cost of the product but on the efficiency of its absorption. Published cost-benefit analyses assume equal bioavailability for all calcium sources. Some published studies have suggested that there are differences in both the bioavailability and cost of the major calcium supplements.

Design: Randomized four period, three-way cross-over comparing single doses of off-the-shelf commercial calcium supplements containing either calcium carbonate or calcium citrate compared with a no-load black and with encapsulated calcium carbonate devoid of other ingredients; subjects rendered fully vitamin D-replete with 10 μ g/day 25(OH)D by mouth, starting one week prior to the first test.

Subjects: 24 postmenopausal women

Methods: Pharmacokinetic analysis of the increment in scrum total and ionized calcium and the decrement in scrum iPTH induced by an oral calcium load, based upon multiple blood samples over a 24-hour period; measurement of the rise in urine calcium excretion. Data analyzed by repeated measures ANOVA. Cost calculations based on average retail prices of marketed products used in this study from April through October, 2000.

Results: All three calcium sources (marketed calcium carbonate, encapsulated calcium carbonate and marketed calcium citrate) produced identical 24-hour time courses for the increment in total serum calcium. Thus, these were equally absorbed and had equivalent bioavailability. Urine calcium rose slightly more with the citrate than with the carbonate preparations, but the difference was not significant. Serum iPTH showed the expected depression accompanying the rise in serum calcium, and there were no significant differences between products.

Conclusion: Given the equivalent bioavuilability of the two marketed products, the cost benefit analysis favors the less expensive carbonate product.

INTRODUCTION

There is general acceptance of the importance of achieving adequate calcium intakes throughout life, and in most adults effort in that regard means taking some form of calcium supplement. Over half the women enrolled in the Women's Health Initiative reported using supplements, and that figure rose to nearly 60% in women over age 70 [1]. While calcium supplementation has generally been considered a cost effective intervention [2,4], much depends upon the cost of the preparation. Thus Torgerson and Kanis, in the UK, calculated that calcium was not cost effective for a preparation they priced at \sim \$0.50/g in current dollars [5]. Lowering that cost modestly produced a more favorable relationship. Rendich *et al.* [4] found that calcium supplementation at 1200 mg/day and a cost of \$0.10-0.12/g was cost effective for all US women 75 years of age or older when calculated against the costs of care associated only with hip fracture. If the endpoint was increase in bone mineral density and its associated lower total fracture risk, then calcium supplementation was cost effective even with universal supplementation of all US men and women 65 years of age or older. An additional consideration, given virtually no attention to

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date, involves factoring in bioavailability of the calcium source. Most, if not all, analyses to date have assumed equivalent bioavailability for different salts and different consumer formulations. Recent publications by Heller *et al.* [6,7] suggested that this might not be the case. The authors reported absorbability for a calcium citrate supplement superior to that of a commercially marketed calcium carbonate product. Since the two salts, in pure form, had been shown in several studies to be absorbed equally well [8–10], a question arose as to whether differences in pharmaceutical preparation of marketed products might have interfered with or enhanced the absorbability of one or the other preparation. Such absorptive effects, if they exist, would alter cost effectiveness calculations, once calcium *acnually delivered* into the blood stream becomes the basis for the computation.

Accordingly we set out to compare two commercial supplements, using standard pharmacokinetic methods, both with one another and with non-pharmaceutical calcium carbonate ingested without excipients. This communication describes the results of this investigation. Additionally, we then used the bioavailability data to calculate the costs associated with providing the two commercially available calcium salts to the US population at greatest risk of hip fracture.

MATERIALS AND METHODS

Subjects

Subjects were 24 postmenopausal women aged 56.1 ± 7.1 years and in good general health. Their BMI was 29.3 \pm 5.2 kg/m². Thirteen subjects were receiving estrogen replacement therapy, and the remaining 11 were not. One was African-American; the others were Caucasian. Subjects taking calcium supplements were asked to abstain throughout the course of the study, starting at least one week in advance of the first test. Additionally, subjects were counseled by our research dietitian to hold calcium from dietary sources to under 400 mg/day, mainly by avoiding all dairy products. Also, they were instructed to avoid high sodium foods (such as commercial fast foods and canned soups or soup mixes) starting two days prior to and including each test day. To eliminate any variability in absorptive performance due to vitamin D insufficiency or to seasonal change in vitamin D status, all subjects were given 10 µg 25(OH)D₃ (Calderol®, Organon, West Orange, NJ)/day starting one week before the first test and continuing throughout the study. This dose is approximately equivalent to 1000 IU (25 μ g) of cholecalciferol, but produces a rapid elevation of serum 25(OH)D, in contrast with the five month time-to-equilibrium required when using cholecalciferol. Further, this dose is the amount required, at Omaha's latitude, to bring serum 25(OH)D concentration up to 32 ng/mL (80 nmol/L), a level widely considered to be the lower limit of physiological normal. The study was approved by the Creighton University

240

Institutional Review Board, and each subject gave written consent.

Design

The study was a four-period, three-way randomized crossover, within-subject design, with each individual receiving Os-Cal® (a product manufactured by GlaxoSmithKline and consisting of calcium carbonate derived from oyster shell), Citracal® (a product manufactured by Mission Pharmacal and consisting of calcium citrate), a gelatin capsule containing precipitated calcium carbonate or an empty gelatin capsule (the blank). The test source was ingested midway through a standard light breakfast containing two pieces of Italian-style white bread (Center-baked from unenriched flour), toasted and buttered, together with a cup of coffee, tea or water (with artificial sweetener if desired), plus additional water to ensure adequate urine volume. Blood samples were taken at 0, 1, 3, 5, 7, 9, 12, and 24 hours for measurement of total and ionized calcium and parathyroid hormone (PTH). Urine was collected in two pools, from 0 to 5 hours, and from 5 to 24 hours, and was analyzed for calcium, creatinine and sodium. Calcium sources were given only on the test day and only at the breakfast meal. The noon meal was provided by Center staff between the 5 and 7 hour blood draws and was designed to be low in both calcium and sodium. The evening meal was ingested between the 9 and 12 hour blood draws. Tests were separated typically by seven days; in this way the entire suite of studies was completed for most subjects within a 22-day period so as to minimize temporal variability in absorptive performance.

Test Sources

For the two commercial products (Os-Cal® and Citracal®), the sources were purchased from a retail pharmacy. The labeled content of elemental calcium for the Os-Cal® was 500 mg, plus 200 I.U. of vitamin D (Control No. 9K2228; exp. date 11/01). In order to approximate the load size of the Os-Cal®, the Citracal@ dose required a combination of two different formulations, one labeled to contain 200 mg elemental calcium (Lot 9D12; exp. date 4/02) and the other 315 mg plus 200 I.U. vitamin D (Lot 9E86; exp. date 5/01). Precipitated calcium carbonate was prepared in the Center's laboratory by dissolving reagent grade calcium chloride in distilled water, heating to 80°C with stirring and adding a slight stoichiometric excess of a heated aqueous solution of sodium carbonate, timed so that the reaction was completed within one minute. The resulting precipitate was collected on a fritted glass filter, washed with deionized water to remove adsorbed sodium chloride, dried at 90°C overnight, ground in a mortar and packed loosely into tared gelatin capsules in sufficient quantity to provide a 500 mg calcium load per dose. All preparations were chemically analyzed; actual ingested loads of calcium were as follows: for Os-Cal®, 503 mg; for Citracal®, 516 mg, and for precipitated calcium carbonate, 497 mg.

VOL. 20, NO. 3

Analytical Methods

Calcium in serum, urine and the ingested sources was analyzed by atomic absorption spectrophotometry (AAnalyst 100, Perkin-Elmer, Norwalk, CT), creatinine in urine by an auto analyzer method (Chiron Express Plus, Ciba Corning Diagnostics, Medfield, MA) and sodium in urine by an ion selective electrode method (Cobas Integra, Roche Diagnostics, Basel, Switzerland). Serum ionized calcium was analyzed under standardized test conditions by an ion selective electrode method (Nova Nucleus, Nova Biomedical, Waltham, MA). Serum immunoreactive parathyroid hormone (iPTH) was measured as the intact molecule by IRMA (Nichols, San Juan Capistrano, CA).

Data Handling and Statistical Analysis

The primary outcome measures were the usual pharmacokinetic variables, area under the curve (AUC), both at five hours and at 24 hours (for both total and ionized serum calcium), as well as the time of maximum serum concentration (Tmax) and the magnitude of the elevation (Cmax). AUC was calculated by the trapezoidal method, and Cmax and Tmax were analyzed both by taking the observed values for concentration and time and by fitting the means of the timed serum increments for each source, using a first-order, two-compartment model with an absorptive delay of 0.5 hours (PKAnalyst; Micro-Math Scientific Software, Salt Lake City, Utah). The curves were plotted, and the pharmacokinetic parameters were calculated, both as the absolute values and as the increment above baseline. Secondary variables were serum iPTH and urine calcium, the latter with and without adjustment for urine sodium. AUC for iPTH was calculated using the same approach as for serum calcium. The sodium adjustment was made in two ways, using a slope factor of either 0.004 mg Ca/mEq sodium or 0.010 mg Ca/mEq Na. In each case adjustment was to the mean sodium excretion value for a given calcium source. The first factor is in the middle of the range reported in the literature for the relationship of urine calcium and sodium [11,12]. The second factor was derived from the slope of urine calcium to urine sodium observed with the blank meal in the subjects of this investigation. For the test calcium sources, urine calcium values are reported as the increment above the calcium content of the corresponding collections obtained on the test day with the blank load.

A standard bioequivalence analysis [13] was performed both on serum total and serum ionized calcium, using AUC from 0 to 5 and 0 to 24 hours, as well as Cmax and Tmax. AUC for serum PTH was also compared. Only the data from the first three periods were used in these bioequivalence analyses, since the treatment in the fourth period (non-pharmaceutical calcium carbonate) was not in random order. A general linear model was fit with the natural logarithm of the variate as the dependent variable, test source, sequence, period and subject nested

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

in sequence as factors and the pre-dose value of the parameter as a covariate. The test sources in this equivalence analysis were Os-Cal®, Citracal® and blank. The sequence (or order) effect was tested using the subject in sequence mean square as the error term. The adjusted mean difference between the carbonate and citrate sources was computed and its 90% and 99% confidence intervals were constructed. The difference and the bounds of the confidence interval were exponentiated to obtain the ratio of the carbonate source mean to the citrate source mean and its confidence interval. As set forth in the applicable FDA Guidelines [13], if the confidence interval for the ratio fell in the range from 0.80 to 1.25, bioequivalence was considered to have been demonstrated.

Cmax and Tmax were compared between treatment groups using paired t tests. Pharmacokinetic parameters for Os-Cal® and Citracal® were each compared to blank using linear contrasts in the general linear model described above. Pharmacokinetic parameters for Os-Cal® and Citracal® were each compared to CaCO₃ using paired t tests. Changes from pre-dose serum concentrations of total and ionized calcium were compared among treatment groups at each time point using doublyrepeated measures ANOVA. Each pairwise comparison among test sources was tested and type I error was controlled at the 5% level using Holm's step-down method. Urine calcium and . sodium-adjusted urine calcium were compared between calcium sources using paired t tests. AUC values for incremental calcium and PTH ratio to baseline were correlated by standard Pearsonian regression. All of these analyses used within-subject differences to make inferences concerning the pharmacokinetic parameters, and in this way full adjustment was made for between-subject differences in absorptive efficiency.

To determine the cost of these supplements, we used the average price at all US outlets and also calculated separately the mass market costs/g of elemental calcium for Os-Cal® and for Citracal® between April and September 30, 2000. The data are provided by AC Nielson. The savings associated with hip fracture reduction were based on a previous analysis of this issue [4] for calcium supplements generally, which in turn used the average 1995 cost per discharged patient with a hip fracture, the size of the age cohort concerned and the fractional reduction in risk derived from published trials of calcium supplementation.

RESULTS

Table 1 presents the pharmacokinetic parameters for both total and ionized serum calcium for the four test sources, and Fig. 1 and 2 show the time courses of total and ionized calcium, respectively. The AUC values for the three calcium sources were all highly significantly different from the blank (p < 0.001), but there was no significant difference between the three calcium-containing sources for either of the AUC values

Parameter	Ds-Cal	Citracal	CaCO ₃	Blank
	n = 24	n = 24	n = 23	<u>n = 24</u>
Total Ca				
Increment AUCs	1.81 ± 0.22	1.88 ± 0.18	1.95 ± 0.15	0.04 ± 0.14
Increment AUC24	6.69 ± 1.07	5.91 ± 1.02	6.39 ± 0.85	-0.05 ± 0.77
Cmax	10.3 土 0.07	10.3 ± 0.08	10.3 ± 0.07	· -
Tmax	4.8 ± 0.51	4.2 ± 0.36	4.1 ± 0.32	~
Ionized Ca				
Increment AUC,	0.83 ± 0.11	1.02 ± 0.11	0.85 ± 0.10	-0.05 ± 0.09
Increment AUC	2.36 ± 0.56	3.58 ± 0.53	2.58 ± 0.46	0.47 ± 0.56
Cmax	5.3 ± 0.02	5.4 ± 0.03	5.3 ± 0.03	_ ·
Tmax	5.1 ± 0.91	4.3 ± 0.43	3.1 ± 0.26	· _

Table 1. Serum	Calcium Pharmaco	kinetic	Parameters	(Mean	<u>+</u>	SEM)	
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AUC is measured in mg/dL · hour, Cmax is measured in mg/dL, Tmax is measured in hours.

or any of the other pharmacokinetic parameters. Also, as Fig. 1 shows graphically, the three sources produced virtually identical total serum calcium time courses, whether expressed as absolute values (Fig, 1A) or as increment above baseline (Fig. 1B). Serum calcium values differed significantly from the corresponding values following the blank load at all time points from 3 to 12 hours for Os-Cal® and from 1 to 9 hours for Citracal@, but there were no significant differences between the calcium sources at any time point. Fig. 2B shows that the incremental elevation of serum ionized calcium for the citrate source was somewhat greater from 5 to 12 hours compared to Os-Cal@ and from 5 to 9 hours compared to the plain calcium carbonate. Consistent with this difference, the AUC24 for ionized calcium (Table 1) was greater for the citrate than for the carbonate preparations. However, given the dispersion of the individual AUC data, none of these differences was statistically significant. There was no effect of the order of the test substance on any of the outcome variables. Similarly, age and estrogen status were also tested and were without effect on the relative absorbabilities of the test calcium sources.

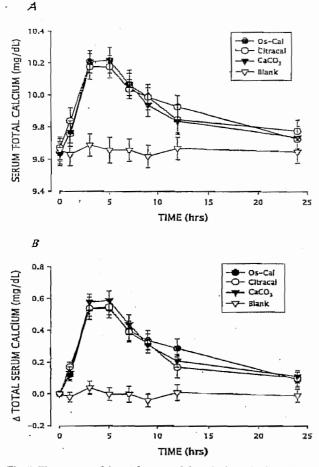
Standard bioequivalence analysis of AUC and Cmax indicated that the carbonate and citrate test sources were bioequiva. lent with respect to serum total and ionized calcium (Table 2). In fact, for all parameters, the ratio of the values for the two sources differed from unity by less than 1%. Both the carbonate and citrate test sources were significantly different from blank. with respect to AUC and Cmax for serum total and ionized calcium. There was no evidence of a difference between the Os-Cal® and CaCO₃ or between Citracal® and CaCO₃ with respect to AUC, Cmax, or Tmax for serum total and ionized calcium, with one partial exception. The time to peak concentration was approximately one hour later with the Citracal® test source than with the CaCO₃ test source (p < 0.05) when using the measured data. Using the mean data fitted to a pharmacokinetic model (a probably better approach), no significant differences were found between the Tmax estimates for any of the sources.

Fig. 3 presents the serum iPTH values for all four sources, first as absolute values (A), then as fractions of the baseline value (B). As is evident, depressions for the three calcium sources were virtually identical, amounting to a drop of $\sim 40\%$ at three hours after calcium ingestion. The AUC₂₄ values for iPTH (not shown) did not differ among the calcium sources, but all three sources did differ significantly from the blank. For both of the carbonate sources (data not shown), but not for the citrate, AUC₂₄ for the iPTH decrement from baseline was significantly correlated with AUC₂₄ for incremental [Ca²⁺] (p < 0.001).

Table 3 presents the urine calcium increments for the three calcium-containing sources above the corresponding urine calcium excretion values for the blank load. Both from 0 to 5 hours and from 5 to 24 hours, the urine calcium increments differed significantly from zero for all three sources. The citrate produced a $\sim 40\%$ greater rise in urine calcium from 5 to 24 hours than either of the carbonate preparations, but, given the wide dispersion of individual values, the difference between sources was not significant. Calcium and sodium excretion were significantly correlated in our subjects as expected (data not shown), and both methods of correcting for sodium excretion slightly reduced the dispersion of the urine calcium values. Nevertheless, the sodium-corrected values, like the uncorrected, did not differ significantly between calcium sources.

The costs of the two supplements and cost:benefit analyses are presented in Table 4. Columns 4 and 8 contain the net benefit of supplementation (in dollars per capita for the population treated). A positive value means that the savings exceed the cost, while a negative value means a net cost. (A negative value is not necessarily bad, since prevention of most diseases usually carries a net cost. Thus the principal value of the net benefit figure is to facilitate comparison between sources.) The citrate source we tested costs between 1.5 and 1.8 times as much as the carbonate source, per gram of elemental calcium. Provision of the carbonate product to all US women 75 years of age and older for 2.83 years was projected to be cost effective,

VOL. 20, NO. 3



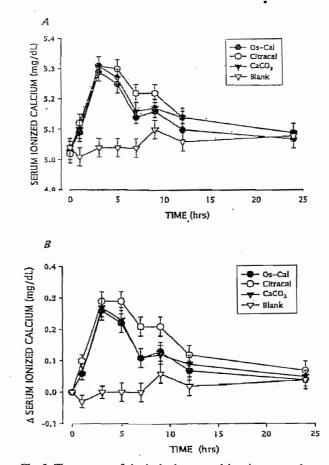


Fig. 1. Time course of the total serum calcium, both as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

saving \$100 million in hip-fracture associated, costs/year; by contrast, the citrate source was not cost effective. If increasedbone mineral density is assumed to be predictive of hip fracture reduction, then universal supplementation of all men and women aged 65 years and older remains cost effective using the

Table 2. Bioequivalence Analysis

Fig. 2. Time course of the ionized serum calcium increment above baseline for the three calcium sources and for the blank load, both as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

carbonate as the calcium source; the net potential benefit is \$478 million/year or a per capita benefit of \$14.26. It is worth noting that the annual cost for providing 1000 mg of elemental calcium as the carbonate preparation is less than \$70 per person.

Parameter	Ratio: Os-Cal to Citracal	90% CI	99% Cİ	Conclusion*
Total Ca AUC,	0.999	0.990, 1.007	0.985, 1.013	bioequivalent
Total Ca AUC24	1.004	0.995, 1.012	0.990, 1.018	bioequivalent
Total Ca Cmax	1.003	0.991, 1.014	0.984, 1.021	biocquivalent
Ionized Ca AUCs	0.994	0.985, 1.002	0.980, 1.008	bioequivalent
Ionized Ca AUC24	0.992	0.986, 0.998	0.982, 1.002	bioequivalent
Ionized Ca Cmax	0.995	0.984, 1.005	0.977, 1.012	bioequivalent

* Blocquivalence is concluded if the 90% confidence interval falls between 0.80 and 1.25. The analysis was performed on log-transformed data, and the difference between adjusted means for Os-Cal and Citracal was exponentiated for the ratio. The upper and lower confidence bounds on the difference between the adjusted means were exponentiated for the upper and lower bounds on the ratio presented in the table.

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

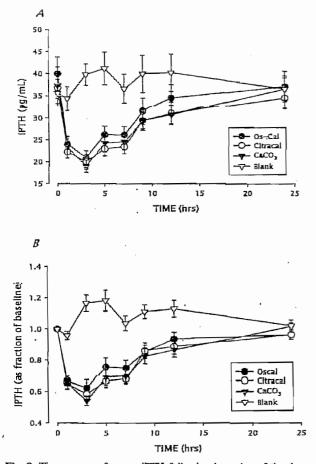


Fig. 3. Time course of serum iPTH following ingestion of the three calcium sources and for the blank load, both as absolute values (A) and as fractional values relative to baseline (B). Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

DISCUSSION

24

Calcium supplementation has been shown, in well-controlled clinical studies, to slow age-related bone loss and reduce the risk of hip and other fractures in middle aged and older men and women. Using U.S. data on the medical costs associated with hip fracture compared to the costs of preventive supplementation with calcium, Bendich *er al.* found that supplementation targeted at those at greatest risk could save over \$2.5 billion/year [4]. However, cost-effectiveness of calcium supplementation depends not only on the cost of the product, but on the efficiency of its absorption. All published cost-benefit analyses to date have assumed not only an average price per gram of calcium regardless of the salt, but equal bioavailability for all calcium sources.

Shangraw [14] had previously shown marked differences in dissolution of calcium supplement preparations, due solely to pharmaceutical formulation differences, and unpublished experience of one of us (RPH) has demonstrated that not all preparations of the same salt exhibit equivalent absorbability. Finally, Heller et al. [7] explicitly raised this question in their recent paper. It is reassnring, therefore, to note that, in this study, Os-Cal@ and the non-pharmaceutic, precipitated calcium carbonate exhibited identical bioavailability values. Thus for at least one marketed calcium carbonate product, pharmacentical formulation does not alter the intrinsic bioavailability of its calcium salt. The same conclusion is probably applicable to the marketed citrate product as well. This is because it did not differ from non-pharmaceutic calcium carbonate in this study and because we had previously shown that the bioavailability values of the pure carbonate and citrate salts were identical [8].

Interestingly, however, and not previously described, several small differences were noted in pattern of response between the citrate and carbonate sources. None was statistically significant in isolation, but taken together, their mutual consistency suggests underlying differences in metabolic response to the two salts. These effects were i) although the rise in total calcium was the same, slightly less of the increment in serum calcium following the carbonate products was carried as the ionized form and slightly more as the bound form, relative to the citrate salt; ii) PTH suppression was slightly greater for the Citracal® than for the Os-Cal®, and the difference approximately coincided with the time points at which the ionized calcium differences were most prominent; and iii) urine calcium excretion in the 5 to 24 hour pool was higher for the Citracal® than for Os-Cal®. The relative depression is shown most clearly in Fig. 4, which plots ionized calcium as a percent of total calcium and shows slightly lower values for the Os-Cal® from 5 to 9 hours. This relative depression may reflect a very slight degree of alkalosis due to exhalation of CO₂ from the carbonate anion, but the reason for the delay after ingestion

Table 3. Urine Calcium Increments after Ingestion of Test Calcium Sources*

	0-5 hours				5-24 hours				
	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM
Os-Cal	23	21	3	22	22	8	22	43	10
Citracal	23	16	3	22	30	10	22	46	9
CaCO ³	21	20	4	20	20	10	.20	38	9

" mg Ca above the corresponding excretion following the blank load,

VOL, 20, N

Page 6

Table 4. Cost: Benefit Analysis of Two Calcium Supplements

		Mcm and women aged \leq 05 years (n = 33,540,000)				Women aged \geq 75 years (n = 9,426,000)			
	No. of tabs p e r bottle	Cost per person 1 year (\$) (1)	Cost for 1 year (\$ million) (2)	Net benefit (\$ million) (3)	Net per-capita benefit (\$) (4)	Cost per person 2.83 year (\$) (5)	Cost for 2.83 year (\$ million) (6)	Net benefit (\$ million) (7)	Net per-capita benefit (\$) (8)
Os-Cal 500 mg Ca + 200 IU D	75	68.62	2,302	140	4.18	194.20	1,831	-169	-17.88
Os-Cal 500 mg Ca + 200 IU D	160	58.54	1,963	478	14.26	165.67	1,562	100	10,65
Citracal 200 mg Ca	200	86.69	2,907	-466	-13.89	245.34	2,313	-651	-69.02
Citracal 200 mg Ca	100	116.25	3,899	-1,457	-43.45	329.01	3,101	-1439	-152.69
Citracal 315 mg Ca + 200 IU D	60	123.02	4,126	-1,684	-50.22	348.16	3,282	-1620	-171.84
Citracal 315 mg Ca + 200 IU D	120	92.02	3,086	645	-19.22	260.44	2,455	-793	-84.12

a is the estimated 1995 population size.

(1) Mass market costs (AC Nielsen) for one year's supply for one person at 1,000 mg elemental calcium per day.

(2) Cost for one year's supply for this population (N × (1)).

(3) Preventable total expenditures (\$2,442 million for 1995 in this population) minus the cost of supplying the catire population for one year (2).

(4) Net benefit divided by the population size ((3) \div N).

(5) Mass market costs (AC Nielson) for 2.83 years' supply for one person at 1,000 mg elemental calcium per day.

(6) Cost for 2.83 years' supply for this population (N \times (5)).

(7) Preventable total expenditures (\$1,662 million for 1995 in this population) minus the cost of supplying the entire population for 2.83 years (6).

(8) Net benefit divided by the population ((7) \div N).

NB: Calculations based on Tables VI, VII. From: Supplemental Calcium for the Prevention of Hip Fracture; Potential Health-Economic Benefits [4]. PapsBKB_Cost Ca Supp (revised 3/5/01)

is unclear. Physiologically, these changes are mutually consistent, since a higher ionized calcium would be expected to lead to a greater depression of PTH release, to an increased filtered calcium load at the kidney and, through lowered PTH, to decreased tubular reabsorption of calcium. Although the greater rise in urine calcium with calcium citrate was not statistically significant in this study, it is worth noting that Heller *et al.* [7] reported a significant loss of calcium in urine following supplementation with calcium citrate (Citracal®) which was not seen with an equivalent dose of calcium carbonate (Os-Cal®).

We had not designed the study to evaluate this issue, and, indeed, we had not anticipated it. Nevertheless, it is worth noting that the finding of a slight increase in calcium excretion with the citrate source is consistent with what we had reported previously [8]. In that earlier investigation, despite identical tracer-based absorption fractions for the citrate and carbonate salts of calcium, there was a tendency for the urine calcium increment to be greater with the citrate than with the carbonate. We had attributed that finding to a calciuric effect of absorbed citrate, but, in view of the ionized calcium findings in this study, it may, instead, reflect a mild alkalotic effect of the carbonate salt.

On a methodologic note, it may be worth mentioning that the increments in urine calcium were substantially more variable than the increments in serum calcium. The coefficients of variation (CVs) of the serum and urine calcium increments at their peak values (3 and 5 hours for serum and 0 to 5 hours for urine), for all calcium sources, were 38% to 60% for serum and 77% to 99% for urine. This roughly twofold greater variability underscores, as we have noted previously [8], the relative

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

weakness of using the rise in urine calcium to estimate absorptive performance, particularly for loads as small as 500 mg.

For this study, the retail cost per 1000 mg of ingested calcium was between \$0.16 and \$0.20 for the marketed calcium carbonate product and between \$0.24 and \$0.38 for the marketed calcium citrate product. Since both sources exhibited equivalent bioavailability, it is clear that the carbonate source was the less expensive of the two *per unit of absorbed calcium* and would therefore exhibit a more favorable cost-benefit relationship in a cost-effectiveness analyses such as set forth in Table 4. Additionally, although not usually considered in cost benefit analysis, the greater calcium density of carbonate-based

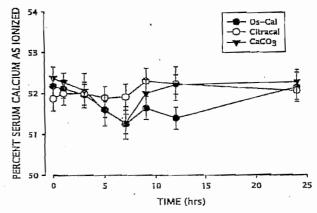


Fig. 4. Time course of serum ionized calcium expressed as a percent of total serum calcium for the three calcium sources. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

products means that fewer pills are needed to achieve a desired supplement intake, a factor known to influence patient compliance [15].

In this study we used 25(OH)D as a rapid and efficient means of ensuring approximately equivalent vitamin D status in all subjects. Such treatment would not be a part of population-level supplementation, and its costs are, accordingly, not a part of our calculations. Vitamin D is contained in both of the supplements tested here, and its cost is, therefore, already factored into the analysis summarized in Table 4.

While we tested only two commercially available products in this analysis, our purpose was not so much to contrast these two specifically as to use them as examples for a type of calculation and analysis that should be performed for all marketed calcium supplement products. It was beyond the scope of this project to undertake an exhaustive survey of different pharmaceutical formulations, although we believe this should be done. It is a matter of commonplace experience that there are many other calcium products available, at least some of which explicitly meet the USP disintegration and dissolution stundards for calcium supplements (and therefore can be presumed to have a bioavailability comparable to what we found here). Their prices range from as low as \$0.09 per 1000 mg to as much as \$0.53. Lacking bioavailability data for most of these products, it is uncertain whether any of them would exhibit an advantage over the products tested here.

In conclusion, based upon bioavailability, cost and clinical efficacy, calcium carbonate, in the form of Os-Cal®, would appear to be a good choice for calcium supplementation in a US population at risk for both low bone mineral density and hip fracture.

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REFERENCES

 Jackson RD, LaCroix A, Cauley J, McGowan J: WHI calcium and vitamin D trial baseline monograph. Annala Epidemiol (submitted) 2000.

- Chrischilles EA: Public health implications of interventions to promote calcium intrake: cost-benefit considerations. Paper presented to the NIH Consensus Development Conference on Optimal Calcium Intake, June 1994, Washington, DC.
- Eddy DM, Johnson Jr CC, Cummings SR, Dawson-Hughes B, Lindsay R, Melton III LJ, Slemenda CW: Osteoporosis: Review of the evidence for prevention, diagnosis and treatment and costeffectiveness analysis. Osteoporos Int 8(Suppl 4):S1-S88, 1998.
- Bendich A, Leader S, Muhuri P: Supplemental calcium for the prevention of hip fracture: potential health-economic benefits. Clin Ther 21:1058-1072, 1999.
- Torgerson DJ, Kanis JA: Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. Q J Med 88:135-139, 1995.
- Heller HJ, Stewart A, Haynes S, Pak CYC: Pharmacokinetics of calcium absorption from two commercial calcium supplements. J Clin Pharmacol 39:1151-1154, 1999.
- Heller HJ, Greer LG, Haynes SD, Poindexter JR, Pak CYC: Pharmacokinetic and pharmacodynamic comparison of two calcium supplements in postmenopansal women. J Clin Pharmacol 40:1237-1244, 2000.
- Heaney RP, Dowell MS, Barger-Lux MJ: Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 9:19-23, 1999.
- Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS: Gastrointestinal absorption of calcium from milk and calcium salts. N Engl J Med 317:532-536, 1987.
- Recker RR: Calcium absorption and achlorhydria. N Engl J Med 313:70-73, 1985.
- Itoh R, Suyama Y: Sodium excretion in relation to calcium and hydroxyproline excretion in a healthy Japanese population. Am J Clin Nutr 63:735-740, 1996.
- Nordin BEC, Need AG, Morris HA, Horowitz M: The nature and significance of the relationship between urinary sodium and urinary calcium in women. J Nutr 123:1615-1622, 1993.
- Center for Drug Evaluation and Research, Food and Drug Administration, US Dept of Health and Human Services: Statistical procedures for bioequivalence studies using a standard twotreatment crossover design, 1992. http://www.fda.gov/cder/ guidance/index/htm
- Shangraw RF: Factors to consider in the selection of a calcium supplement. In "Proceedings of the 1987 Special Topic Conference og Osteoporosis," Public Health Rep S104:46-49, 1989.
- Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR: The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 150:1881-1884, 1990.

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