JCI The Journal of Clinical Investigation

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J Clin Invest. 1965;44(12):1960-1967. https://doi.org/10.1172/JCI105302.

Research Article

Journal of Clinical Investigation
Vol. 44, No. 12, 1965

The Influence of Age on the Intestinal Absorption of ^{47}Ca in Women and Its Relation to ^{47}Ca Absorption in Postmenopausal Osteoporosis *

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The literature is still controversial regarding the intestinal absorption of calcium in osteoporosis, with conflicting reports of decreased absorption (1–4), increased absorption (5–7), and normal absorption (8–10). The apparent discrepancies in these reports may stem from *a*) the absence of a common isotopic absorption test wherein oral ^{47}Ca doses of uniform specific activity are administered in the fasting state, *b*) wide variations in the amount and chemical form of the administered stable calcium carrier, *c*) inadequate identification of the osteoporotic disease process and its differentiation from osteomalacia, *d*) the lack of sufficient age-matched nonosteoporotic controls for comparison, and *e*) wide variations in dietary calcium intakes, which prohibit adequate comparison between individual reports.

The lack of reported investigations in humans relating the absorptive capacity of the intestine to age and to osteoporosis and the availability of a simplied oral isotopic test of calcium absorption (11) prompted an evaluation of calcium absorption in 59 normal women of various ages and in 16 women with severe osteoporosis.

Methods

The normal population consisted of 59 women with an average age of 40 years (range, 12 to 85 years). This group included 15 nonosteoporotic elderly postmenopausal females with an average age of 67 years (Table I). Sixteen women ranging in age from 58 to 87 years (average age, 70 years) with severe osteoporosis were also subjected to absorption studies (Table II).

The osteoporotic subjects were selected on the basis of normal serum calcium, inorganic phosphorus, alkaline phosphatase, and total protein levels (Table II), and lateral spinal roentgenograms with the following pathologic changes: *a*) collapse of one or more dorsal spinal vertebral bodies, *b*) resorption of the horizontal trabeculae and accentuation of vertical trabeculae of the vertebral bodies, *c*) biconcavity of the dorsal spinal vertebrae, and *d*) absence of appreciable spondylosis or annular osteophytes. Patients without collapsed vertebrae were excluded from this study. Aside from the above radiographic spinal changes the osteoporotic women were in good physical condition and fully ambulatory.

Serum calcium, phosphorus, and alkaline phosphatase determinations were also made on all normal subjects according to previously published methods (11). The menstrual cycles of all premenopausal women were characterized by normal periodicity and rhythmicity. All of the subjects were studied during periods of hospitalization after 14 to 21 days of adaptation to constant weighed calcium intakes ranging from 170 to 380 mg per day.

After a 12- to 15-hour overnight fast and 1 hour before breakfast, subjects were given 5 to 10 μc of $^{47}CaCl_2$ (SA greater than 150 mc per g calcium) orally in 5 ml of distilled water containing 20 mg of calcium as $CaCl_2$. Plasma, urine, and stool samples were collected and analyzed for ^{47}Ca content according to previously described techniques (11). Cumulative ^{47}Ca content of stools after the oral dose was measured for 12 consecutive days in 6-day pools in all osteoporotic patients and in 15 normal postmenopausal subjects. Since negligible and undetectable amounts of absorbed ^{47}Ca are re-excreted into the gastrointestinal tract after a small oral ^{47}Ca test dose (2, 11, 12), the cumulative 12-day stool radioactivity was considered to be another independent measurement of ^{47}Ca absorption.

Results

Normal subjects. Figure 1 summarizes the characteristic plasma ^{47}Ca activity curve of the 59 normal subjects. Increments in blood radioac-

* Submitted for publication May 21, 1965; accepted August 19, 1965.

Supported in part by grants from the U. S. Public Health Service (Clinical Research Center grant FR-41, National Institute of Arthritis and Metabolic Diseases grant 06404, and trainee grant 2A-5211) and by Atomic Energy Commission contract AT(30-1)-3174.

† Recipient of a Career Research Development Award of the National Institute of General Medical Sciences (6-K3-GM-22, 676-01A1).

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TABLE I

^{47}Ca content of blood and feces in normal elderly postmenopausal women after oral ^{47}Ca

Subject	Age	Ca intake	Serum Ca	Serum P	Serum alkaline phosphatase	Time in minutes after oral dose							12-day fecal ^{47}Ca	Average urinary Ca*
						15	30	45	60	120	180	240		
	years	*mg/day*	*mg/100 ml*	*mg/100 ml*	*Bodansky U*	*% Administered dose/L plasma*							*% Administered dose*	*mg/day*
P.S.	55	240	10.1	4.1	4.5	0.75	1.23	1.97	2.38	1.97	1.73	1.69	54.1	72
R.S.	55	258	9.7	3.9	3.9	0.41	1.42	1.77	2.26	2.30	1.99	1.58	49.8	121
Q.B.	58	360	9.5	3.9	4.4	0.26	1.09	1.37	1.45	1.30	1.27	1.02	57.9	32
M.T.	60	197	8.6	4.2	2.1	0.50	0.71	0.98	1.35	1.20	1.14	1.00	60.1	49
A.N.	60	230	9.7	3.5	2.7	0.95	1.02	1.37	1.61	1.70	1.39	1.22	42.7	57
E.M.	61	380	10.1	3.9	3.0	1.05	1.21	1.76	2.42	2.01	1.85	1.79	57.9	101
M.G.	62	210	9.7	4.0	3.1	0.98	1.31	1.98	2.75	2.76	2.34	1.95	51.0	22
W.J.	64	340	9.6	3.5	2.9	0.36	1.41	1.50	1.65	1.68	1.43	1.21	58.3	65
M.S.	65	190	9.4	3.7	2.8	0.89	1.32	2.01	2.48	2.35	1.96	1.71	56.1	43
Q.H.	65	210	8.4	4.0	3.1	0.66	1.50	1.75	1.82	1.66	1.57	1.47	47.7	59
R.C.	76	230	9.1	3.6	3.7	0.57	0.98	1.63	1.95	1.77	1.63	1.44	60.7	92
M.S.	79	260	10.2	3.8	4.0	0.77	0.89		1.65	1.39	1.21	1.17	62.1	112
F.M.	80	310	9.3	3.9	2.9	0.47	1.09	1.53	1.97	1.86	1.75	1.65	52.8	75
J.B.	82	250	8.9	4.0	3.9	0.71	0.85	1.01	1.15	1.17	1.02	0.94	64.1	40
R.K.	85	270	8.8	4.4	4.0	1.00	1.23	1.79	1.95	1.38	1.27	1.19	58.7	39
Mean	67	262	9.4	3.9	3.4	0.69	1.15	1.60	1.92	1.77	1.57	1.40	55.6	65
± SE						±0.05	±0.04	±0.07	±0.10	±0.12	±0.08	±0.07	±1.4	±6

* Average of six consecutive 24-hour collections.

TABLE II

^{47}Ca content of blood and feces in osteoporotic postmenopausal women after oral ^{47}Ca

Subject	Age	Ca intake	Serum Ca	Serum P	Serum alkaline phosphatase	Time in minutes after oral dose							12-day fecal ^{47}Ca	Average urinary Ca*
						15	30	45	60	120	180	240		
	years	*mg/day*	*mg/100 ml*	*mg/100 ml*	*Bodansky U*	*% Administered dose/L plasma*							*% Administered dose*	*mg/day*
L.B.	74	260	9.0	3.8	3.8	0.58		1.28	1.67	1.40	1.19	1.04	58.7	44
A.B.	62	380	9.7	4.0	4.1	1.21	1.81	1.97	2.03	1.83	1.73	1.67	47.8	17
M.B.	58	210	9.8	3.7	2.0	0.48	1.20	1.45	1.64	1.53	1.30	1.19	52.0	37
L.G.	72	197	10.0	4.4	2.9	0.60	1.46	1.58	1.65	1.68	1.56	1.42	63.0	64
J.L.	75	180	9.3	3.7	1.6	1.32	1.56	2.85	2.87	2.56	2.27	2.08	57.8	31
J.D.	63	210	8.9	4.0	4.6	0.44	1.01	1.55	1.74	1.55	1.33	1.18	58.9	101
L.G.	69	380	10.2	3.8	3.7	0.59	1.57	2.30	2.66	2.58	2.15	2.05	57.3	96
C.C.	87	295	10.0	3.9	3.9	0.71	1.18	1.52	1.59	1.42	1.39	1.29	51.7	72
A.R.	70	220	9.3	3.4	2.1	0.27	1.25	1.93	2.14	2.16	1.81	1.58	42.6	65
Q.K.	72	170	9.6	4.1	2.9	1.59	1.85	2.91	2.71	2.22	2.16	2.14	49.7	49
S.K.	58	360	10.1	3.8	3.9	0.22	0.84	1.23	1.29	1.17	1.00	0.86	59.1	12
A.M.	84	280	9.0	4.1	4.0	0.23	0.62	0.88	1.19	1.11	1.01	0.67	60.1	61
B.C.	68	295	9.4	3.9	4.1	0.79	1.45	1.86	2.02	2.04	1.71	1.59	55.0	80
R.G.	73	200	10.2	3.6	2.7	0.41	0.85	1.88	2.08	2.03	2.00	1.95	59.2	97
J.Q.	70	250	10.0	3.6	2.7	0.42	0.81	0.98	1.06	1.11	1.04	0.96	48.0	88
A.C.	71	210	9.8	3.8	4.2	0.26	0.72	0.94	1.09	1.05	1.04	0.93	55.3	29
Mean	70	270	9.6	3.9	3.3	0.63	1.22	1.69	1.84	1.72	1.54	1.41	54.8	59
± SE						±0.08	±0.08	±0.12	±0.11	±0.09	±0.08	±0.07	±1.3	±6

* Average of six consecutive 24-hour collections.

tivity were observed after the oral ^{47}Ca dose for the first hour followed by a gradual decline in the subsequent 3 hours. The average 1-hour plasma ^{47}Ca activity of the 59 subjects was 2.33 (range, 1.15 to 3.90) % dose per L. Correlation between age and 1-hour ^{47}Ca plasma activity as illustrated in Figure 2 was highly significant ($p < 0.001$) and could be described by the regression line, $y = 3.06 - 0.017\ x$, where y = 1-hour ^{47}Ca plasma activity and x = age in years.

The concentration of ^{47}Ca in plasma and the percentage of the administered dose recovered in the feces 12 days after oral ^{47}Ca administration to 15 elderly nonosteoporotic postmenopausal females is illustrated in Table I. Peak plasma ^{47}Ca activities were observed at 1 hour in 10 of the 15 subjects with a gradual decrease in radioactivity during the subsequent 3 hours. The average 1-hour plasma value was 1.92 (range, 1.15 to 2.75) % dose per L plasma. Cumulative fecal radioactivity ranged from 42.7 to 64.1% of the administered dose with a mean of 55.6. In 8 of the 15 normal postmenopausal subjects urinary calcium was less than 60 mg per day. Daily urinary calcium excretion ranged from 22 to 121 mg in these subjects with an average of 65 mg per day. No significant correlation was noted between dietary calcium and urinary calcium (Table I).

Osteoporosis. The results of the oral ^{47}Ca test in 16 patients with severe osteoporosis are recorded in Table II. As in the normal population, plasma ^{47}Ca activity rose steadily for the first hour

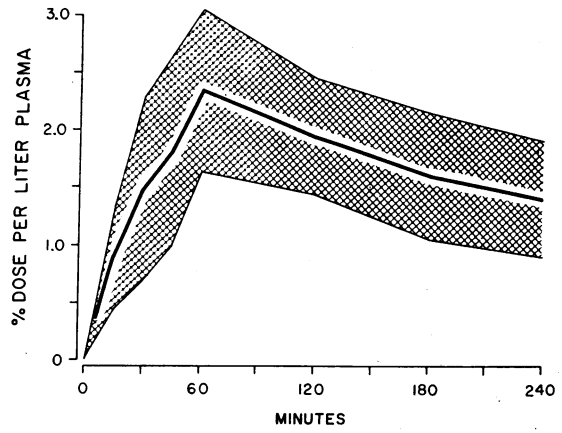

FIG. 1. FOUR-HOUR PLASMA ^{47}CA ABSORPTION IN 59 NORMAL SUBJECTS. The shaded area represents 2 SD below and above the population mean represented by the dark line.

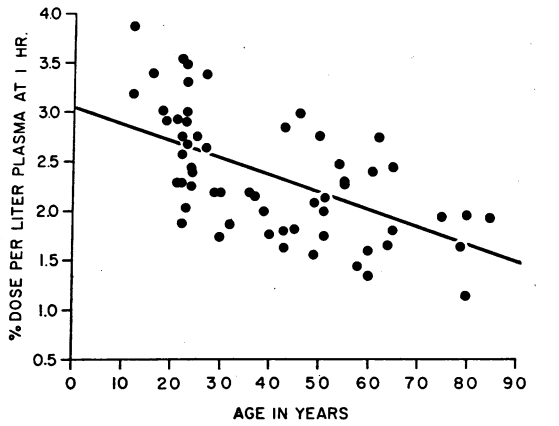

FIG. 2. REGRESSION SLOPE AS DETERMINED BY THE METHOD OF LEAST SQUARES AND SCATTERGRAM OF 1-HOUR PLASMA ^{47}CA VALUES IN 59 NORMAL FEMALE CONTROL PATIENTS.

after the oral dose in 12 of the 16 patients and gradually declined in the subsequent 3-hour period. The mean ± SE of the 1-hour plasma ^{47}Ca activities of the osteoporotic patients was 1.84 ± 0.11, a value which is suggestively lower than that for the age-matched control population (1.92 ± 0.10, Table I and Figure 3). This difference was not significant ($p > 0.5$). Conversely if the mean 1-hour plasma ^{47}Ca activity of 26 younger premenopausal females (2.67 ± 0.07, Figure 3), ranging in age from 16 to 32 years, is compared with that of the osteoporotic population, a significant difference is apparent with $p < 0.001$.

The amount of unabsorbed fecal ^{47}Ca in the osteoporotic women (42.6 to 63.0% administered dose) was also similar to values obtained in the age-matched nonosteoporotic control population with no significant differences between the means of the respective groups ($p > 0.5$). As in the normal elderly population (Table I) a good negative correlation was noted between 12-day fecal ^{47}Ca concentrations and 1-hour plasma ^{47}Ca values with $p > 0.05$ in both instances. On calcium intakes similar to those of the normal postmenopausal age-matched controls, the osteoporotic subjects average daily urinary calcium was 59 mg (range, 12 to 101 mg per day), with 7 of the 16 women excreting less than 60 mg per day (Table II).

Discussion

The availability of a simplified oral isotopic procedure for an *in vivo* analysis of calcium absorp-

tion contributed to the successful pursuit of the present clinical study. The reproducibility, specificity, and diagnostic implication of this method have been described in a previous communication (11). Because of the reported significant correlation between 1-hour plasma ^{47}Ca activity after an oral dose and other independent measurements of calcium absorption, 1-hour plasma ^{47}Ca values were used as relative calcium absorptive indexes and analyzed accordingly. The good negative correlation between unabsorbed fecal ^{47}Ca and 1-hour plasma ^{47}Ca values in both the elderly controls and osteoporotic subjects confirms these earlier observations. Despite protocols wherein patient preparation, specific activity of the ^{47}Ca oral test dose, and biological sampling were identical, the mean 1-hour plasma ^{47}Ca value of the 59 normal subjects in the present investigation (2.33% dose per L) is higher than our previously reported mean normal values of 1.69% dose per L (11). The calcium intake of the normal population in the present study was relatively low (range, 170 to 380 mg per day), whereas 17 of the 21 normal patients of an earlier communication were on intakes of 500 mg or greater (11). Since calcium absorptive efficiency by the intestine reportedly varies inversely with dietary calcium (12–18), the higher plasma ^{47}Ca levels in the normal subjects of this investigation are attributed to the lower calcium intake of the population.

The observed relationship between age and calcium absorption noted in Figure 2 confirms the results of animal experimentations of Henry and Kon (19), Harrison and Harrison (20), Lengemann, Comar, and Wasserman (21), and Taylor, Bligh, and Duggan (22), all of whom showed that the amount of calcium absorbed varies inversely with the age of the animal. Similar observations have been made by Kimberg, Schachter, and Schenker during *in vitro* studies with isolated loops of rat intestine (23). Recently some preliminary evidence in man that the intestinal absorption of calcium decreases with advancing age has also been cited by Nordin (24) and Harrison (13). The age-^{47}Ca absorption dependence relationship cannot relate to pathological malabsorption of calcium per se, since as illustrated in Figure 1 and Table I the 4-hour plasma ^{47}Ca pattern of pre- and postmenopausal normal subjects characteristically displayed a normal rapid rise in plasma activity with peak values at 1 hour followed by a definite fall in the subsequent 3-hour period (11). This is in marked contrast to the reported ^{47}Ca absorptive pattern of malabsorption syndromes with the characteristic delay in the appearance of plasma ^{47}Ca after an oral dose and

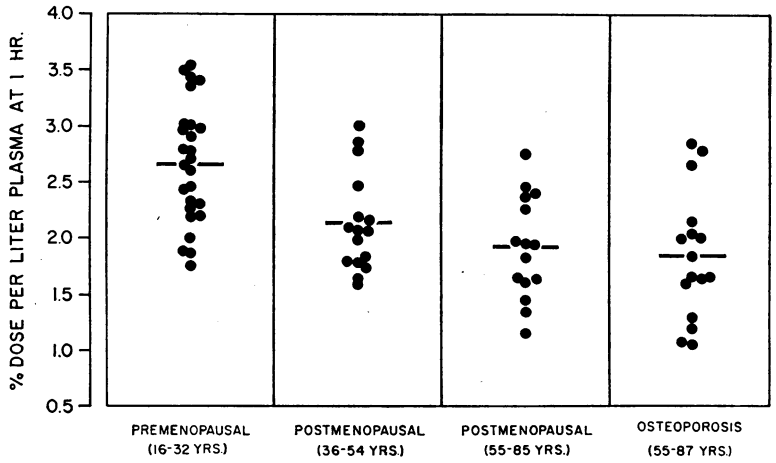

FIG. 3. ONE-HOUR PLASMA ^{47}Ca CONCENTRATION IN 59 NORMAL POSTMENARCHAL FEMALE SUBJECTS AND 16 OSTEOPOROTIC SUBJECTS. The horizontal bar in each group represents the mean of the respective population. Calculated mean values for each age group are as follows: 16 to 32 years, 2.67 ± 0.07% dose per L plasma; 36 to 54 years, 2.14 ± 0.09; 55 to 85 years (normal postmenopausal), 1.92 ± 0.10; 55 to 87 years (osteoporosis), 1.84 ± 0.11.

only minimal decline in plasma radioactivity once peak values have been attained (11). Since the rate of gastric emptying and gastrointestinal motility are not altered in elderly persons (25) and since age-dependent absorption relations have also been reported for other substances such as strontium (26), magnesium (27), D-xylose (28), and vitamins B_{12} (29) and A (30), the observed decrease in calcium absorption with advancing age is considered to represent the normal physiological intestinal adjustment to senescence.

This relationship between calcium absorption and age proves especially noteworthy in view of recent studies implicating calcium malabsorption as one of the etiological factors of postmenopausal osteoporosis. Caniggia, Gennari, Bianchi, and Guideri have recently reported decreased calcium absorption in 13 osteoporotic females when compared to a control population (1). Of the five normal subjects, three were 31 years of age or younger in contrast to the 46- to 85-year age distribution of the osteoporotic subjects. Similarly, Jaworski, Brown, Fedoruk, and Seitz noted decreased ^{47}Ca absorption in a 59-year-old untreated osteoporotic woman while she was receiving a calcium intake of 650 mg per day when compared to a control population (age range, 23 to 41 years) on calcium intakes ranging from 600 to 2,200 mg per day (2). DeGrazia and Rich have also reported decreased calcium absorption in a 50-year-old osteoporotic patient, but five of the seven control subjects were 45 years of age or younger (15). Figure 3 illustrates the necessity for concomitant age-matched control studies during an analysis of ^{47}Ca absorption in osteoporosis, since a significant decrease in ^{47}Ca absorption is apparent when an elderly osteoporotic population is compared to a younger control group. The normal patterns of ^{47}Ca absorption observed in the osteoporotic females and the strikingly similar unabsorbed ^{47}Ca content of 12-day cumulative fecal collection in both osteoporotic and age-matched control subjects (Tables I and II) suggest that ^{47}Ca absorptive mechanisms are normal (for the respective age) during low calcium intakes in postmenopausal osteoporosis. These conclusions based primarily on a comparison of osteoporotic females and nonosteoporotic age-matched controls on similar low dietary calcium intakes are consistent with recent limited observations of Bronner and his associates (10), Spencer, Menczel, and Lewin (31), and Nordin (4), who used a variety of techniques.

The observed poor correlation between dietary and urinary calcium in osteoporotic patients and elderly nonosteoporotic controls (Tables I and II) during periods of low calcium intake confirms previous observations of Nordin (9, 32) and Whedon (33). In the present study, however, no significant increments in urinary calcium were observed in the osteoporotic group when compared to their age-matched controls on similar dietary intakes.

Previous investigations in animals and man suggest that an accelerated catabolism of bone mineral with gradual decrease in bone density is a common if not general accompaniment of senescence (34–36). The observed inverse relationship between age and ^{47}Ca absorption in the present study may therefore relate significantly to the normal proportionate decrease in bone density with advancing age cited by Baylink, Vose, Dotter, and Hurxthal (37), Moon and Urist (38), Heuck and Schmidt (39), and Smith and Frame (40). The normal intestinal absorption of calcium by osteoporotic females despite reported marked disproportionate decrease in bone density (37) suggests that postmenopausal osteoporosis probably results from factors other than alterations in calcium absorption. The mechanisms that initiate and perpetuate this disorder are still ill defined. Whether postmenopausal osteoporosis is due primarily to a decreased production of anabolic hormones as originally suggested by Albright, to an abnormal increase in bone catabolism, or to an abnormal utilization of absorbed calcium still remains uncertain.

Summary

The intestinal absorption of orally administered ^{47}Ca has been quantitated in 59 normal female subjects with ages ranging from 12 to 85 years and in 16 postmenopausal osteoporotic women after adjustments to low calcium intakes. A significant inverse correlation between 1-hour plasma ^{47}Ca levels and age was observed. Patients with osteoporosis demonstrated a normal ^{47}Ca absorption pattern when compared to 15 age-matched nonosteoporotic controls with no significant differences in 1-hour plasma ^{47}Ca levels or cumulative

12-day fecal ^{47}Ca excretion. The implication of these findings and their correlation with age-dependent changes in bone density are discussed.

Acknowledgments

The authors gratefully acknowledge the assistance of Miss Madeline A. Nowacki. We are also grateful to Mrs. Estelle Saplicki, dietitian, and Mr. Peter Ignatenko, medical illustrator, of the Clinical Research Center.

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