A Retrospective Study of a Calcium Agent (E-Ca) Using Data on Bone Mineral Density Obtained by DXA Method

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Abstract. *Aim: We performed a retrospective analysis of a calcium hydroxide-containing calcium agent (TACHIKAWA DENKAI CALCIUM™ : E-Ca) based on data of bone mineral density obtained by dual-energy X-ray absorptiometry (DXA) to clarify the relationship between bone mineral density and E-Ca intake on an empty stomach in those who regularly use E-Ca. Results: We found the percentage of volunteers with their age-matched (AM) values of above 100% to be 89%, and also a moderate positive correlation between AM values and the intake period of E-Ca. Conclusion: Our findings demonstrate that AM values can be used as an effective indicator assessing osteogenesis by regularly administrated calcium agents which exert their effects after long-term use.*

Many countries in the world are facing an aging society with a declining birthrate, and it is urgently necessary that an effort is made to prevent diseases such as osteoporosis and dementia. Since prevention requires self-control of abnormal calcium metabolism which occurs in elderly people, a simple, user-friendly indicator of bone mineral density is needed. Some reports describe the therapeutic aspects of calcium agents as follows (1, 2): the safe maximum intake of calcium is 2,300 mg/day for both men and women; the recommended intake of calcium for the treatment of osteoporosis is 800 mg/day or above; the recommended intake of calcium supplement to compensate for insufficient intake of calcium from the diet is 1,000 mg/day. Regarding therapeutic aspects, calcium agents are assessed as being effective for the retention of bone mineral density of young people (grade A), but as only slightly effective for the retention of bone mineral density in the treatment of osteoporosis (grade C). Generally, calcium agents come in the form of a salt combined with an acid such as calcium carbonate, calcium citrate, and calcium gluconate, the single dose of these calcium agents amounting several hundred milligrams. In patients with achlorhydria, absorption of calcium differs according to the form of salt and intake status; for example, it is said that calcium carbonate is poorly absorbed during fasting, while calcium citrate is well absorbed (3). We hypothesized that intake of a very small amount of calcium ion on an empty stomach may have some effect on absorption and metabolism of calcium consumed regularly and on bone metabolism; we have tried to identify a simple indicator of bone mineral density to verify the hypothesis shown in Figure 1 (4). Recently, we found a new study and introductory article entitled "Stomaching calcium for bone health" the concept of which is similar to that of our hypothesis (5, see also 6). We therefore conducted a retrospective survey in volunteers who have regularly used a calcium agent for many years to determine its relationship to changes in bone mineral density.

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Key Words: Bone mineral density, AM value, TACHIKAWA DENKAI CALCIUM™ (E-Ca), calcium hydroxide, dual-energy X-ray absorptiometry, DXA method.

Materials and Methods

Materials. As a calcium agent, we used TACHIKAWA DENKAI CALCIUM™ (Morita Pharmaceutical Ind., Ltd, Tokyo, Japan) (E-Ca) which is calcium hydroxide and has been commercially available as an OTC medicine for about 40 years. The details regarding E-Ca as given by the manufacturer are as follows: Composition: Each 100 ml of this product contains 80 mg calcium. Dosage and administration: In adults, the daily dose of 40 ml should be taken on an empty stomach in 2 or 3 divided doses. The dose for

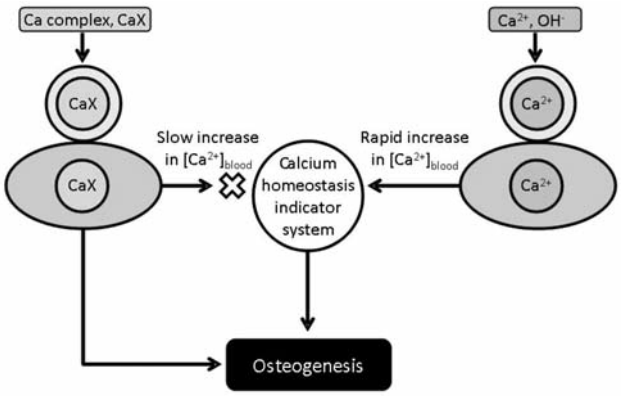

Figure 1. *Postulated mechanism for the action of low-dose of Ca^{2+} (calcium hydroxide solution) taken on an empty stomach.*

children is half that for adults. Indications: Calcium supplementation for calcium deficiency or as nutritional supplement; calcium supplementation for lactating women and growing children.

Preliminary survey. We investigated the dosage, administration and intake period of E-Ca in groups of men and women who have ingested E-Ca for many years and measured bone mineral density at the same time point to investigate the effect of E-Ca on bone mineral density. Bone mineral density was measured in the distal radius, the distal one third of the radius or lumbar vertebrae (L2-L4) by the dual-energy X-ray absorptiometry (DXA) method (7), an internationally accepted method.

Main survey. We conducted a questionnaire and bone mineral density measurement in a group of twenty-five female volunteers who have regularly ingested E-Ca for many years and who participated in the survey after explanation of the purpose of the survey. Bone mineral density was uniformly measured in the distal radius by the DXA method.

Questionnaire survey. We investigated the background factors of the volunteers such as diseases, therapeutic agents, lifestyle, and nonessential grocery items and their intake status of E-Ca. The purpose of this survey was to identify volunteers with clear reasons for a decrease in bone mineral density; the volunteers with factors which may interfere with the assessment of the effect of E-Ca (see Table I) were excluded from the survey.

Analysis. YAM values, termed as an indicator of bone mineral density compared with young adults, and AM values, termed as an indicator of bone mineral density compared with gender- and age-matched controls, both of which were obtained from results by the DXA method, were analyzed for their correlation with factors such as age, intake period, dose, and intake frequency.

Results

Bone mineral density of a small number of male volunteers taking E-Ca. In all male volunteers, bone mineral density was measured in the distal one third of the radius. Half of the volunteers were 40 years old or younger; the other half of the volunteers were 50 years old or older (Table II). Although the dose of E-Ca ranged from 20 ml to 80 ml, most volunteers (7 volunteers) received 40 ml, which is designated as the usual dose. All male volunteers fell into the category of normal (YAM value of 80% or above). The correlation between age and bone mineral density (YAM values and AM values) is shown in Figure 2. YAM values decreased with age as a matter of course and showed a moderate negative correlation (r=–0.6336) because the YAM value by definition is a value made in comparison with young adults. AM values, which are values made in comparison with people of the same sex and same age, also decreased with age, with their rate of decrease being smaller than that of YAM values, showing a weak negative correlation (r=–0.4042). When looking at AM values, nine out of twelve volunteers had AM values of above 100%. We therefore investigated the correlation between the dose of E-Ca (ml) and AM value in the young adult group (40 years old or younger) and the more elderly group (50 years old or older) and obtained a strong positive correlation between the dose and AM values in both groups (r=0.9913 for 40 years old or younger volunteers; r=0.9174 for 50 years old or older volunteers) (Figure 3).

Bone mineral density of a small number of female volunteers taking E-Ca. Bone mineral density was measured in lumbar vertebrae (L2-L4) (volunteer number in order of age: 1, 3, 4), distal radius (volunteer number: 2, 6, 9), and distal one third of the radius (volunteer number: 5, 7, 8). The female volunteers received 30 to 40 ml of E-Ca once or twice daily (Table III). Four volunteers fell into the category of normal; four, the category of osteopenia; and one, the category of osteoporosis. The relationship between age and bone mineral density (YAM values and AM values) is shown in Figure 4. Similar to the results of male volunteers mentioned above, their YAM values showed a strong negative correlation with age (correlation coefficient r=–0.7420), while their AM values showed a slight increasing tendency (correlation coefficient r=0.1095), and seven out of nine volunteers had an AM value of above 100%. We therefore investigated the relationship between AM values and the number of daily intake to obtain the mean AM value of 95% for volunteers who received once-daily E-Ca (n=2) and that of 109% for volunteers who received twice-daily E-Ca (n=7). There was a tendency for the number of intakes to be directly proportional to AM values. The relationship between AM values and the intake period for those who received E-Ca twice daily showed a strong positive correlation (r=0.8364) (Figure 5).

Bone mineral density of large number of female volunteers taking E-Ca without clear reasons for a decrease in bone mineral density. Next, we investigated the bone mineral density of a larger number of female volunteers taking E-Ca

Table I. *Negative factors for evaluation of E-Ca.*

1. Treatment for osteoporosis
2. Treatment for disease thought to cause a bone decrease such as chronic renal failure, hyperthyroidism, bone metastases of a malignant tumor, transformable lumbar vertebra syndrome, lumbar vertebra syndrome, or multiple myeloma
3. Medication thought to cause a bone decrease such as steroid or gonadotropin antagonist
4. Not eating breakfast regularly
5. Not drinking E-Ca in the morning
6. Rapid decrease in body weight
7. Heavy smoker or cohabitation with a heavy smoker

in consideration of the negative factors that influence the bone density. Seven volunteers (number 11, 12, 14, 15, 16, 18 and 25) were excluded from the analysis on the basis of the following factors, which are considered to induce bone mineral density reduction: "osteoporosis and its associated diseases", "no breakfast in the morning", "no intake of E-Ca in the morning", "sudden weight decrease", and "smoking" (Table IV). With regard to the eighteen volunteers selected; ten fell into the category of normal; four, the category of osteopenia; and four the category of osteoporosis (Table V). The relationship between age and bone mineral density (YAM values and AM values) is shown in Figure 6. Similar to the results of the preliminary survey, YAM values decreased with age with a strong negative correlation (r=–0.7370), while AM values seemed to show a moderate positive correlation with age (r=0.4817). We found that sixteen out of eighteen volunteers had an AM value of above 100% as shown in Table V. The relationship between the AM values and intake period was shown in Figure 7. Six out of eight volunteers had AM values of 120% or more after 100 months of intake, with a moderate positive correlation between the intake period and AM value (r=0.6056).

Table II. *YAM and AM values of male volunteers taking E-Ca.*

Volunteer number	Age (years)	Consumption of E-Ca			Bone mineral density	
		Dosage (ml/day)	Frequency (per day)	Period (months)	YAM (%)	AM (%)
1	26	40	1	14	95	95
2	23	40	2	3	103	104
3	27	40	1	1	109	109
4	34	40	1	3	107	107
5	54	60	2	96	103	106
6	27	50	1	12	109	110
7	56	40	1	120	95	98
8	24	60	1	24	119	120
9	60	20	1	240	96	101
10	53	80	3	1	108	111
11	64	40	1	66	101	108
12	71	40	2	288	85	94

Discussion

We analyzed the data on bone mineral density of the female osteoporosis patients who took E-Ca 20 ml twice a day, one hour before breakfast and supper respectively, to determine the effect of E-Ca intake at regular dose in 2009 (4). Among three volunteers, one volunteer had been on E-Ca for only 6 months and two volunteers had been on E-Ca and bisphosphonate (BP) for more than 5 years. In all of them, bone mineral density (YAM values and AM values) was elevated over time. Based on this finding, we decided to conduct this retrospective survey. The survey reveals that the longer the period of E-Ca intake, the higher the AM value is, suggesting that the AM value can be used as an indicator of the effect of E-Ca on osteogenesis.

The dose of this agent is about 1/30 that of calcium used to prevent and treat osteoporosis. Since this agent comes as a free calcium ion solution, it moves to the small intestine without changing its form, and is absorbed mainly by active transport. In 1990, Yamaguchi *et al*. investigated the effect of E-Ca on blood calcium level and osteogenesis, in an experiment in which E-Ca at 16 mg/kg was orally administered to rats (8). In this experiment, an excessive amount of calcium, an amount equivalent to total daily intake, was administered at once. As a result, the blood calcium level rose by 10% in 20 to 30 minutes after administration, and returned to baseline in 60 minutes. In an experiment in which E-Ca was administered 7 consecutive days in rats whose movement of the femur was restricted by skeletal unloading, increased bone mineral content in the femur and increased serum alkaline phosphatase were observed (9).

Bone mass of humans increases until the age of 20 years when it reaches its peak, is maintained at the same level until the fifth decade of life, then starts to decrease. There is a difference in the rate of decrease in bone mass between men and women. In men, bone mass decreases by 10% for every about 10 years in the fifth decade of life and thereafter. In women, bone mass decreases more rapidly than in men because decreases in female hormones due to menopause

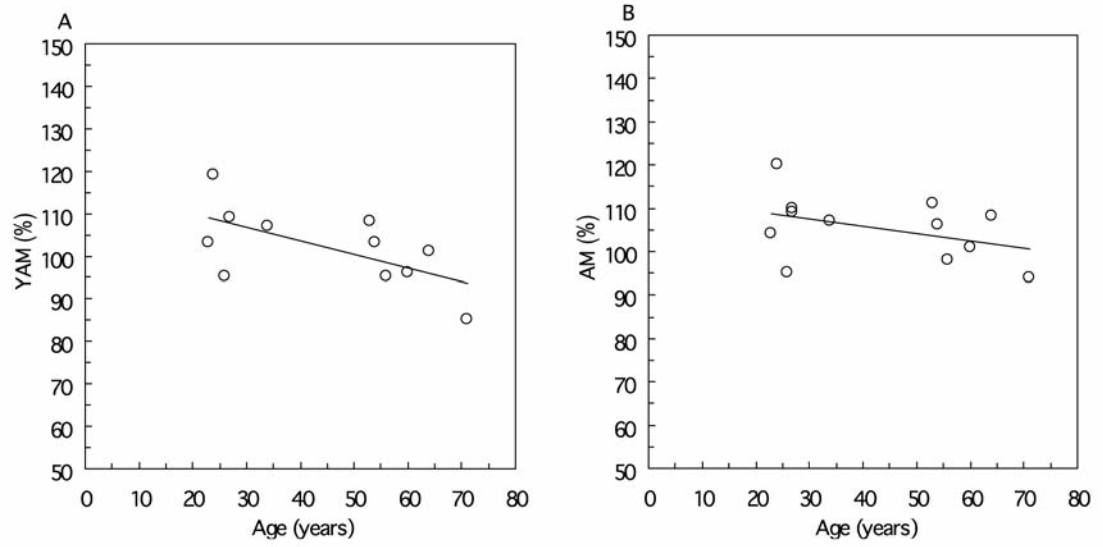

Figure 2. *Correlation between bone mineral density and age according to A: YAM value and B: AM value.*

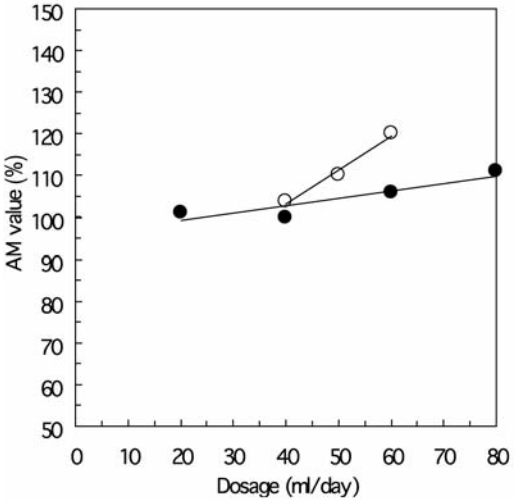

Figure 3. *Correlation between AM value and E-Ca dosage according to age group (open symbols: under 40 years old volunteers, closed symbols: over 50 years old).*

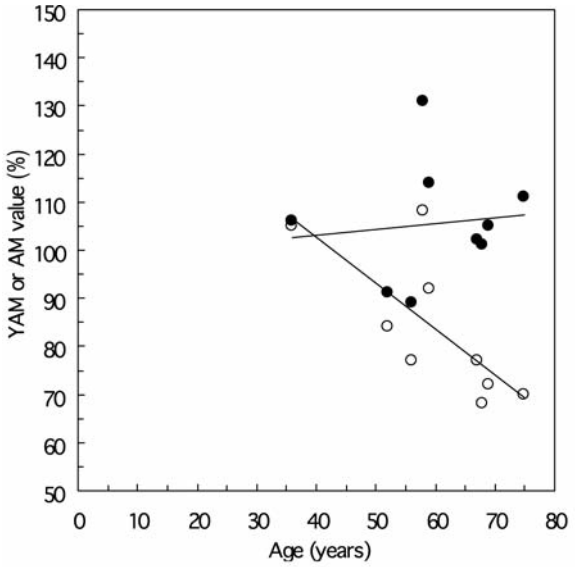

Figure 4. *Correlation between YAM and AM values and age (open symbols: YAM value, closed symbols: AM value).*

mitigate the inhibition of osteoclasts. Changes in bone mass as above can be found from changes in YAM value over time. Calcium is an important nutrient taken in from drinking water or food, insufficient Ca intake resulting in osteoporosis. Osteoporosis is associated with a high risk of compression fracture. In general, a YAM value lower than 70% falls into the category of osteoporosis. Intake of sufficient calcium from an early age and subsequent achievement of a high peak bone mass are especially important to prevent osteoporosis in older age. This is supported by the following surveys in postmenopausal women: a survey published in 1966 shows that the incidence of osteoporosis is higher in the residents of areas with a low intake of calcium and protein (10); a survey published in 1979 indicates that the residents of areas with a high intake of calcium have higher intakes of energy, lipid, and protein, a significantly higher bone mass, and a lower incidence of fracture (lower by 50%) compared to those in areas with lower intake of calcium (11); and a survey published in 1990 reports that supplementation of 500 mg/day of calcium to menopausal women with a low intake of

Table III. *YAM and AM values of female volunteers taking E-Ca.*

Volunteer number	Age (years)	Consumption of E-Ca			Bone mineral density		Measurement site
		Dosage (ml/day)	Frequency (per day)	Period (months)	YAM (%)	AM (%)	
1	36	60	2	28	105	106	Lumbar vertebrae (L2-L4)
2	59	80	2	276	92	114	Distal radius
3	56	40	1	147	77	89	Lumbar vertebrae (L2-L4)
4	52	60	2	24	84	91	Lumbar vertebrae (L2-L4)
5	68	40	1	300	68	101	Distal one third of the radius
6	67	60	2	64	77	102	Distal radius
7	69	80	2	38	72	105	Distal one third of the radius
8	75	60	2	62	70	111	Distal one third of the radius
9	58	80	2	300	108	131	Distal radius

Table IV. *Vital data of female volunteers taking E-Ca.*

Volunteer number	Chronic disease/syndrome	Other medication	Negative factor (no. from Table I)
1	-	Lactomin,	
2	-	-	
3	Pleurisy, pleurae caries, uterine fibroids, pancreatitis	Pravastatin, magnesium oxide, Zaltoprofen	
4	Appendicitis, uterine fibroids,	Amlodipine, Levothyroxine sodium	
5	Hypertension, gastritis, dyslipidemia	Benidipine hydrochloride, Toughmac, Ecabet sodium, Simvastatin, Lansoprazole	
6	Gastritis	-	
7	Malignant lymphoma, colorectal cancer	Etizolam	
8	Hypertension	Amlodipine	
9	Diabetes mellitus	Glimepiride, roxatidine acetate hydrochloride	
10	Hypertension	Olmesartan medoxomil, Amlodipine, ethyl icosapentate	
11	-	-	4
12	Uterine fibroids, transformable lumbar vertebra syndrome syndrome,	-	2
13	Stomach cancer	Diclofenac sodium, Rebamipide, Misoprostol, Loxoprofen sodium	
14	-		7
15	Hypertension, combined lumbar spinal canal stenosis	Amlodipine	5
16	Hypertension, lung cancer, peptic ulcer, lumbar vertebra syndrome	Famotidine, Rebamipide, Amlodipine	2
17	Hypertension	Amlodipine	
18	Arrhythmia, tinnitus	Etizolam, Verapamil hydrochloride, Propranolol hydrochloride	6
19	Hypertension	-	
20	Diabetes mellitus, angina pectoris	-	
21	Hypertension	Amlodipine, Candesartan cilexeti	
22	Gastritis	Famotidine	
23	Hypertension	Amlodipine	
24	-		
25	Hypertension	Candesartan cilexeti	7

calcium (400 mg/day) inhibits a decrease in bone mass of spine, femoral neck, and radius (12).

Regarding the effect of calcium supplementation on bone metabolism, a survey published in 1999 suggests that it induces apoptosis of mature osteoclasts (13), and a survey published in 2005 indicates that an increase in intake of calcium enhances not only function of osteoblasts but also induction of apoptosis of osteoblasts, resulting in decreased osteogenesis (14). These findings suggest that when extracellular calcium level is increased by deteriorated

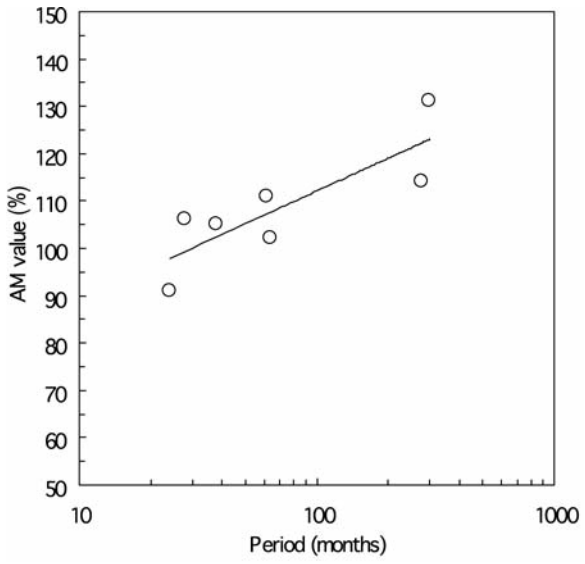

Figure 5. *Correlation between AM value and period time of E-Ca use.*

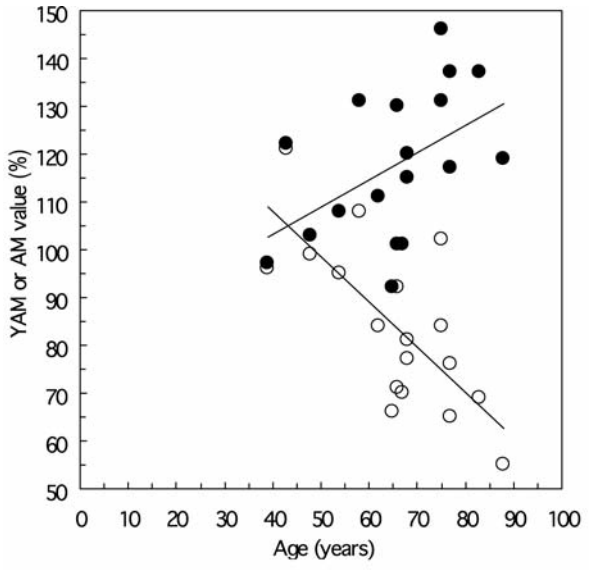

Figure 6. *Correlation between YAM and AM values and age (open symbols: YAM value, closed symbols: AM value).*

Table V. *YAM and AM values of female volunteers taking E-Ca.*

Volunteer number	Age (years)	Consumption of E-Ca			Bone mineral density	
		Dosage (ml/day)	Frequency (per day)	Period (months)	YAM (%)	AM (%)
1	48	40	1	96	99	103
2	58	80	2	288	108	131
3	83	40	1	182	69	137
4	88	50	2	63	55	119
5	77	30	1	180	65	117
6	75	40	2	154	102	131
7	67	10	1	104	70	101
8	68	30	1	144	81	120
9	75	50	1	68	84	146
10	54	50	1	40	95	108
13	68	60	2	20	77	115
17	65	120	3	42	66	92
19	77	50	1	210	76	137
20	66	50	1	241	92	130
21	66	40	1	56	71	101
22	39	100	2	20	96	97
23	62	30	1	44	84	111
24	43	40	2	77	121	122

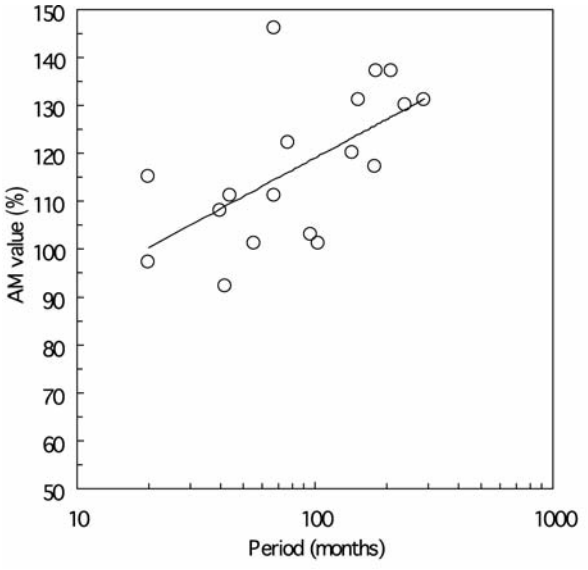

Figure 7. *Correlation between AM value and period time of E-Ca use.*

calcium metabolism, aggressive calcium intake may induce a risk of increased apoptosis in osteoblasts. Thus, a safe maximum calcium intake is defined as 2,300 mg/day for both men and women (15). Based on an experiment in Japanese, it is reported that calcium balance becomes negative if the intake is less than 800 mg/day (16). Interestingly, a report in 2006 shows that calcium agents intended for treatment of osteoporosis are effective for preservation of bone mineral density in the young (grade A), but are not so effective in the elderly (grade C). Namely, calcium absorption in the small intestine, when calcium agents were given in the form of salts combined with acids such as calcium carbonate, calcium citrate, and calcium gluconate, decreased due to a decrease of gastric acids with aging. In patients with achlorhydria,

absorption of calcium differs according to the form of salt and conditions of intake: for example, it is said that during fasting, calcium carbonate is poorly absorbed but calcium citrate (3) and calcium gluconate are well absorbed (6).

In conclusion, we demonstrate in our retrospective analysis of E-Ca that AM values can be used as an effective indicator for assessing regularly administered drugs such as calcium agents which exert their effects after long-term use.

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