Milk Consumption Decreases Activity of Human Serum Alkaline Phosphatase: A Cross-Sectional Study

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Since the Japanese have not reached the recommended daily allowance (RDA) for calcium (600 mg), milk is recommended as a Ca-rich food to increase Ca intake and prevent osteoporosis in Japan. To determine whether milk consumption influences Ca/bone metabolism in the Ca-deficient population, relationships between milk consumption and serum alkaline phosphatase (Al-P) activity were analyzed in 3,098 premenopausal and 1,182 postmenopausal women and 13,141 men aged 30 to 69 years. Milk consumption was classified into no/yes groups by a self-administered questionnaire that asked "Do you drink a glass of milk (180 to 200 mL) or more everyday?". Regardless of age or sex, the "yes" group had a lower activity of serum Al-P than the "no" group. Milk consumption decreased the activity to a greater degree in women, especially perimenopausal/postmenopausal women, than in men. These results were confirmed in a multivariate analysis considering age, body mass index (BMI), and smoking and drinking habits as confounding factors. Although menopause obviously increased serum Al-P activity in perimenopausal women, it could not influence the effects of milk consumption on the activity. These results suggest that milk has osteostatic effects on humans via a mechanism different from that of estrogens. Milk consumption, even one glass per day, may be an easy and effective strategy for prevention of osteoporosis in the Ca-deficient population, especially perimenopausal/postmenopausal women.

THE JAPANESE have not reached the recommended daily allowance (RDA) for calcium (600 mg). The mean Ca intake was 531 mg/d in the Japanese National Nutrition Survey of 1990.[1] In our previous survey[2] in Gifu-shi in 1991, the mean Ca intake (543 mg/d) for 210 women aged 24 to 76 years was also less than the RDA. The low Ca intake in the Japanese is partly due to low consumption of dairy foods rich in Ca. Daily consumption of milk and other dairy products was 120 and 11 g/d, respectively, and Ca intake from dairy foods was only 142 mg/d in the Nutrition Survey.[1] The Japanese are a Ca-deficient population. Osteoporosis, defined as a decrease of bone mass, is a multifactorial disease that occurs with aging, especially in postmenopausal women. Since chronic Ca deficiency is a risk factor for osteoporosis,[3-5] milk as a Ca-rich food is recommended to increase Ca intake and prevent osteoporosis in Japan. However, milk/Ca supplements in the diet for prevention of osteoporosis are controversial.[6,7] Approximately half of human serum alkaline phosphatase (Al-P) activity is derived from osteoblasts in healthy adults.[8,9] In perimenopausal women, rapid bone loss and increases in serum Al-P activity with menopause have been reported,[10-14] and an inverse correlation between serum Al-P activity and bone density has been found.[15] Therefore, serum Al-P activity may be an easy index for human bone health. Thus, to investigate biologic effects of milk consumption on bone metabolism in Ca deficiency, we analyzed relationships between milk consumption and serum Al-P activity using health-check data in a general population.

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SUBJECTS AND METHODS

All data on the subjects were taken from medical records in the Gifu Prefectural Center for Health Check and Health Promotion.

Study Subjects

Gifu-Prefecture had a population of 2.06 million in 1990, and 7,750 women and 17,520 men aged 16 to 88 years visited the Center for a health check from April 1990 to March 1991. Of these, 4,280 women and 13,141 men were selected as study subjects using the following six conditions: (1) age 30 to 69 years, (2) no present medical treatment (to remove effects of present disease and medical treatment on serum Al-P activity), (3) no medical history of gynecologic disease (to remove effects of the disease on menstruation in women), (4) no medical history of malignancy, (5) fasted serum sample without hemolysis, and (6) complete data.

The mean age for study subjects was 45.6 years in women and 46.0 in men. Milk consumption of the subjects was classified into "no" or "yes" groups by a self-administered questionnaire that asked "Do you drink a glass of milk (180 to 200 mL) or more everyday?". Women were also asked to report whether they had experienced menopause. The number of subjects according to age, sex, menopause status, and milk consumption is listed in Table 1. Body mass index (BMI) calculated from body height and weight ranged from 14.9 to 36.6 kg/m^2 (mean, 22.4) in women and from 15.0 to 38.2 (mean, 23.1) in men. Subjects were also classified into nonsmoker/smoker and nondrinker/drinker groups by self-report: 4,023 women (94.0%) and 6,389 men (48.6%) were nonsmokers, and 3,387 women (79.1%) and 3,165 men (24.1%) were nondrinkers.

Serum Analysis

Fasted venous blood was taken from the subjects at 9 to 10 AM, and serum Al-P activity was analyzed by the German Society for Clinical Chemistry (GSCC) method[16] using a commercial kit (Autosera ALP; Dai-ichi, Tokyo, Japan) and an autoanalyzer (CL-7300; Shimadzu, Kyoto, Japan) on the sampling day. The interassay coefficient of variation for nine determinations was less than 1.9%, and the accuracy was checked by a commercial control serum (Control Serum I and II; Wako Jyunyaku, Osaka, Japan).

Table 1. Number of Subjects by Age, Sex, Menopause Status, and Milk Consumption

Age (yr)	Milk Consumption								
	Premenopausal Women			Postmenopausal Women			Men		
	No	Yes	Total	No	Yes	Total	No	Yes	Total
30-34	117	203	320	0	0	0	608	479	1,087
35-39	464	334	798	0	0	0	1,341	711	2,052
40-44	679	311	990	3*	3*	6	2,182	913	3,095
45-49	457	281	738	50	25	75	1,733	838	2,571
50-54	162	84	246	233	157	390	1,220	735	1,955
55-59	2*	3*	5	252	188	440	842	678	1,520
60-64	1*	0	1	112	83	195	383	277	660
65-69	0	0	0	32	44	76	107	94	201
Total	1,882	1,216	3,098	682	500	1,182	8,416	4,725	13,141

*These small groups are not shown in Fig 1.

Table 2. Multiple Regression Analysis of Age, BMI, Milk Consumption, and Smoking and Drinking Habits on Serum Al-P Activity (partial regression coefficient)

Independent Variable	Dependent Variable: Serum Al-P Activity (IU/L)		
	Premenopausal Women (n = 3,098)	Postmenopausal Women (n = 1,182)	Men (n = 13,141)
Age (yr)	0.86‡	0.79†	0.36‡
BMI (kg/m²)	1.07‡	0.00 NS	−0.07 NS
Milk consumption (no = 0, yes = 1)	−5.56‡	−12.14‡	−5.39‡
Smoking habit (non-smoker = 0, smoker = 1)	0.98 NS	8.13 NS	9.61‡
Drinking habit (non-drinker = 0, drinker = 1)	−4.54‡	−8.61*	−11.32‡
Intercept	63.12	139.68	147.30
R^2	0.051‡	0.028‡	0.040‡

Abbreviation: NS, nonsignificant.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Statistical Analysis

Age-specific serum Al-P activity (geometric mean) was compared between no and yes groups on milk consumption by t test with or without Cochran's correction (Fig 1). Then, considering age, BMI, and smoking and drinking habits as confounding factors, multiple linear regression analysis with serum Al-P activity as a dependent variable in premenopausal/postmenopausal women and all men was performed to detect effects of milk consumption on Al-P activity (Table 2). Finally, interactive effects of milk consumption and menopause status on the activity were checked in multiple regression analysis in 1,449 women aged 45 to 54 years (Table 3). The computer program PC-SAS (SAS Institute, Cary, NC) was used, and statistical significance is denoted by P less than .05 for all tests.

RESULTS

Age-specific serum Al-P activity (geometric mean) according to sex, menopause status, and milk consumption is presented in Fig 1. In both premenopausal and postmenopausal women, the yes group had lower serum Al-P activity than the no group in any age group. These results were also observed in men. Milk consumption decreased the activity to a greater degree in women (by 4.6 to 30.4 IU/L) than in men (0.6 to 10.3). It particularly decreased the activity in perimenopausal and postmenopausal women aged ≥45 years (by 7.5 to 30.4 IU/L). Multivariate analysis with five factors as independent variables confirmed the lower activity of serum Al-P in the yes group (Table 2). Milk consumption had the largest effects on serum Al-P activity in postmenopausal women. Namely, milk consumption decreased the activity by 5.56 IU/L in premenopausal women, 12.14 in postmenopausal women, and 5.39 in men.

In women aged 45 to 54 years (Fig 1), menopause increased serum Al-P activity by 38.2 to 41.3 IU/L in the no group and by 32.4 to 43.1 in the yes group. Increases in the activity with menopause were almost equal between no and yes groups. Multivariate analysis in women aged 45 to 54 years showed that milk consumption decreased serum Al-P activity by 10.51 IU/L and that menopause increased the

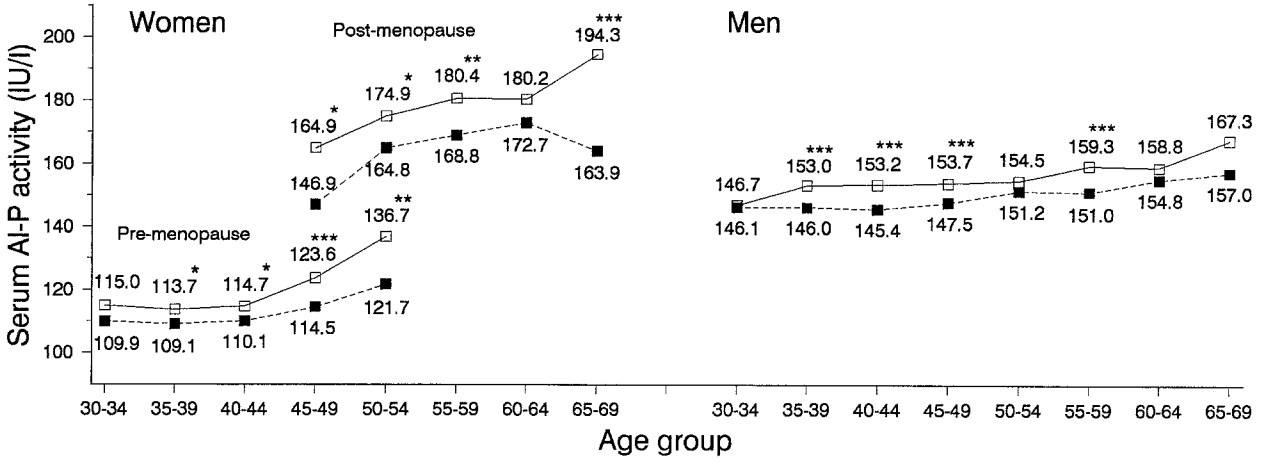

Fig 1. Age-specific serum Al-P activity (geometric mean) according to sex, menopause status, and milk consumption; (□) no group; (■) yes group. *$P < .05$, **$P < .01$, ***$P < .001$: v corresponding yes group.

Table 3. Interactive Effects of Milk Consumption and Menopause Status on Serum Al-P Activity in 1,149 Women Aged 45 to 54 Years (partial regression coefficient)

Independent Variable	Dependent Variable: Serum Al-P Activity (IU/L)
Age (yr)	2.98†
BMI (kg/m²)	0.75*
Milk consumption (no = 0, yes = 1)	−10.51†
Smoking habit (nonsmoker = 0, smoker = 1)	−0.27 NS
Drinking habit (nondrinker = 0, drinker = 1)	−3.2 NS
Menopause status (pre = 0, post = 1)	36.14†
Milk · menopause (interactive effects)	−0.33 NS
Intercept	−28.46
R^2	0.287†

*$P < .05$.
†$P < .001$.

activity by 36.14 (Table 3). Effects of milk consumption on the activity are approximately one third those of menopause. However, no interactive effects of milk consumption and menopause on the activity were found.

In both sexes, slight increases in serum Al-P activity with age were found (Fig 1). In the multivariate analysis, aging's effects on the activity were almost the same between premenopausal and postmenopausal women (0.86 *v* 0.79 IU/L/yr), and aging's effects in men (0.36 IU/L/yr) were less than half those in women (Table 2). BMI was positively correlated with serum Al-P activity in premenopausal women, but not in postmenopausal women or men. Smoking increased serum Al-P activity by 9.61 IU/L in men, but not in women. Drinking decreased serum Al-P activity in both sexes, and the effects were larger in men than in women. The two habits had smaller effects on serum Al-P activity than milk consumption in women, but had larger effects than milk consumption in men.

DISCUSSION

The study showed that the yes group had lower serum Al-P activity than the no group, regardless of age or sex. Milk intake may suppress bone formation, since approximately half of serum Al-P is derived from osteoblasts in healthy adults.[8,9] Bone mass, ie, bone health, depends on the balance of bone resorption and formation.[17] Milk supplementation (24 oz/d) in postmenopausal women improved the balance because it suppressed bone resorption to a greater extent than bone formation.[18] Milk may have osteostatic effects on humans. Ca supplementation (500 mg/d) decreased serum Al-P activity in Ca-deficient children whose pretreatment mean Ca intake was 125 to 337 mg/d.[19] Moreover, Ca supplementation (1,000 to 2,000 mg/d) in perimenopausal women (pretreatment mean Ca intake, 1,150 mg/d) decreased both serum Al-P activity and vertebral bone loss.[20] Also, in a Ca-kinetics study in humans, bone resorption was inversely related to Ca intake.[21] Unfortunately, total Ca intake of the subjects was not surveyed in this study. However, the yes group probably ingests more Ca than the no group, since a glass of milk has approximately 200 mg Ca, one third of the Japanese RDA. The higher Ca intake in the yes group may have decreased serum Al-P activity and may improve bone balance.

Menopausal increases in serum Al-P activity, which may reflect the onset of perimenopausal bone loss,[13,14] were confirmed here. Since menopausal effects on bones are probably due to withdrawal effects of estrogens, estrogens are commonly used for treatment and prevention of perimenopausal/postmenopausal bone loss in the United States and Europe, but this hormone therapy is rare in Japan.[22] The annual Japanese National Nutrition Survey has reported that the mean Ca intake was less than 300 mg/d in 1950. Prepubertal Ca deficiency may be a more important risk factor for osteoporosis.[23,24] If so, the incidence of osteoporosis will rapidly increase in Japan, because the Japanese population that suffered such severe Ca deficiency at prepuberty in 1950 will soon be elderly. Our results suggest that the effects of milk consumption on bone metabolism are approximately one third those of estrogens, and that the mechanism of such effects is different from that of estrogens. Milk, even one glass per day, may be an easy and effective strategy for improvement of bone health in the Ca-deficient population, especially perimenopausal/postmenopausal women.

After human bone mass reaches its peak in the third or fourth decade of life, it gradually decreases with age even in normal subjects.[10-12] The increases in serum Al-P activity with age were larger in women than in men in this study. Not only the lower peak bone mass[25,26] but also larger aging effects in women than in men may increase susceptibility to osteoporosis in women. Although obesity is a protective factor for osteoporosis,[3-5] BMI was positively correlated with serum Al-P activity in premenopausal women (not in postmenopausal women or men). Greater body weight may improve bone balance by stimulating bone formation without increasing bone resorption in premenopausal women. Smoking increased serum Al-P activity in men, but not in women. The negative results in women may be due to the low ratio of smokers (6.0%) in the women. Drinking decreased serum Al-P activity in both sexes. Men had larger effects of drinking on the activity than women, probably because men consume more alcohol than women in Japan. In this way, the two habits had opposite effects on serum Al-P activity, although both smoking and heavy alcohol use (alcoholism) are risk factors for osteoporosis.[3-5] The positive association between social drinking and bone density recently reported[27] is consistent with our results, ie, decreases in serum Al-P activity with drinking. Since individuals with any current disease (including alcoholic hepatic disease) were excluded from our study, almost all of the subjects are probably light or moderate drinkers. Social drinking, ie, light or moderate use of alcohol, may improve human bone health. Drinking and smoking habits are much less frequent and lighter in women than in men in this study and our previous surveys in Gifu-shi.[2,28] Moreover, the two habits had lesser effects on serum Al-P activity than milk consumption and menopause in women. Therefore, the two habits may not be important factors influencing bone health in Japanese women.

We conclude that milk intake is an easy and effective strategy for improvement of bone health and prevention of osteoporosis in Ca-deficient populations. Since bone resorption was not considered here, further epidemiologic studies with indices for bone resorption in general populations are required to reveal the effects of milk consumption and other risk/protective factors for osteoporosis on bone balance.

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