Effects of Calcium Aspartate Anhydrous on Treatment of Osteoporosis

J.F. Tang, Ph.D., Haitian Liu, Ph.D., Qiang Wang, Ph.D., X.S.Bai, Ph.D., Tianlin Lou, Ph.D., Tongge Yang, Ph.D., Haihuan Song, M.D., Qing Zhu, M.D., Q.C. Guo, M.D., Mingkun Zhao, M.D., Baoguo Chen, M.D., Yueshan Xie, M.D., Jiawen Hu, M.D., Haiying Zhou, M.D., Lei Song, M.D., Jun Chen, M.D., and Xiaoming Li, M.D.

ABSTRACT

Background Osteoporosis is a common metabolic bone disease. We conducted a multi-center, double-placebo, double-blind study to verify the effects of calcium aspartate anhydrous on osteoporosis.

Methods 1,306 patients with an initial t-score of –1.5 or lower were randomly assigned to receive calcium aspartate anhydrous (CalAA, 520mg elemental per day) and a placebo, or calcium citrate (1500 mg elemental per day) and vitamin D (1000 IU per day), or two placebos.

Results At 3 months, the bone mineral density (BMD) at the lumbar spine had increased by a mean of 4.07% in the CalAA group, 0.64 percent in the calcium citrate group and there was no significant change in the double-placebo group. The BMD of the total hip had increased by a mean of 3.37 percent in the CalAA group. No significant change was detected in the calcium citrate group or the double-placebo group. At 12 months, lumbar spine BMD had increased by a mean of 5.66 percent in the CalAA group, while the calcium citrate group and the double-placebo group saw decline of 0.51% and 0.75% respectively. Total hip BMD had increased by a mean of 4.11 percent in the CalAA group while there was no significant change in the calcium citrate group. Total hip BMD declined by a mean of 1.17% in the double-placebo group.

Conclusions Calcium aspartate anhydrous increases bone mineral density significantly. Calcium citrate plus vitamin D may help slow down bone loss at the hip.

The exact cause of primary osteoporosis is not clear at present, but it is generally the co-interaction result of a number of factors and links. Most believe that the occurrence of osteoporosis is associated with various factors such as increased age, decreased hormone level, and calcium dysbolism, etc. As for women, particularly for menopausal women, many researchers believe that the occurrence of osteoporosis is closely related to decreased estrogen level and calcium dysbolism. The occurrence of osteoporosis in aged men can also be attributed to multiple factors. Androgens of aged men participate in the process of bone metabolism and play important roles in bone formation and maintenance. In addition, increased secretion of parathormone in the aged men reduces the bone formation but enhances the bone resorption. Kidney degeneration in aged men reduces the activity of hydroxylase, which in turn, decreases calcium absorption in the small intestine, causing negative calcium balance and loss of bone matrix. Attempts have been made to treat osteoporosis with a variety of pharmacological agents, such as estrogens and bisphosphonates. Evidence shows that those therapies have limited success in osteoporosis treatment. Therefore, a more effective method of preventing and treating osteoporosis is desirable.

METHODS

Study Design

In this one-year, multi-center, double-placebo, double-blind study, patients with t-score under –1.5, were randomly assigned to three groups. Group I receives CalAA (4 g per day, 520 mg elemental) and a placebo matching Vitamin D. Group II receives calcium citrate (1,500 mg elemental per day) and Vitamin D (1000 IU per day). Group III was given one placebo matching calcium, and another placebo matching Vitamin D.

Study Profile

A total of 1,306 patients were eligible. The criteria for exclusion were hormone-replacement therapy initiated within the previous year, or the use of bisphosphonates or calcitonin therapy.

Twenty-one patients withdrew before the 3-month visit, and thirty-four withdrew before the 12-month visit. The rate of retention for 12 months was 96.3% in the CalAA group, 95.4% in the calcium citrate group and 95.6% in the double-placebo group. Figure.1 gives details of the study profile.

Bone Density Measurements

Baseline measurements of bone mineral density were obtained immediately after signing of the consent forms. The measurement of bone density was repeated at 3 and 12 months. The primary efficacy endpoints were the percent changes in the bone mineral density of the lumbar spine and the total hip at 3 and 12 months.

Bone density was measured with the use of a dual-energy x-ray absorptiometry (Hologic QDR-4500), and was expressed in grams per square centimeter.

Statistical Analysis

Statistical models were designed to detect differences between the groups in the BMD percentage change from baseline to 3 months and from baseline to 12 months in the spine, the femoral neck, and the hip, with a two-tailed P value of 0.05 and 95% confidence intervals. The primary analyses compared Group I and Group II at 3 months and 12 months. Secondary analyses compared Group I and Group III, Group II and Group III, at 12 months.

RESULTS

Study Population

The groups did not differ significantly in terms of age, sex, or baseline bone density (Figure 1 and Table 1).

Figure 1. Study Profile.

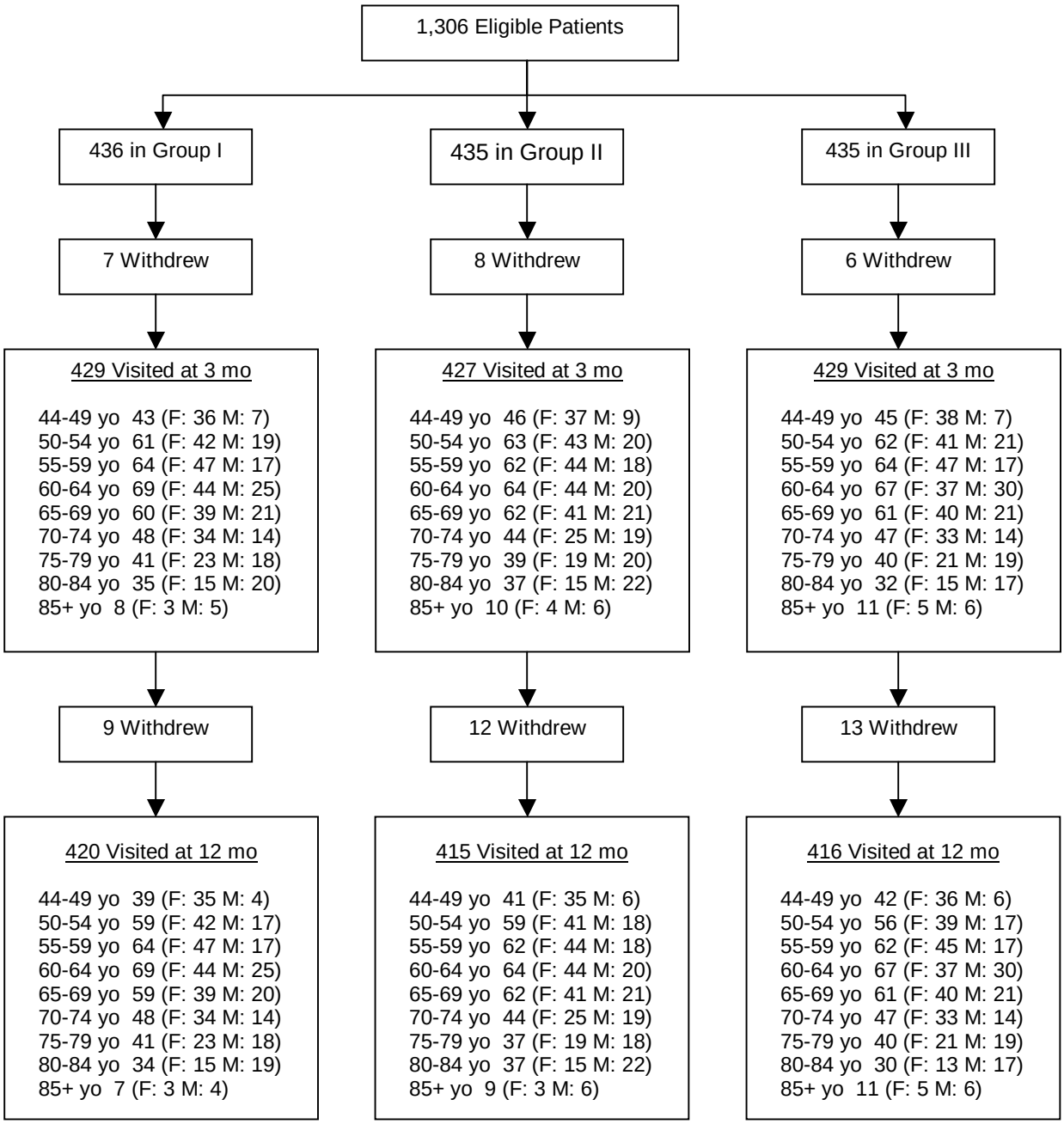


Table 1. Baseline Bone Mineral Density

BMD (g/cm^2)	Group I	Group II	Group III
Lumbar Spine (L1-L4)	0.778±0.16	0.785±0.15	0.797±0.17
Left Femoral Neck	0.631±0.12	0.628±0.14	0.637±0.15
Total Hip	0.682±0.17	0.693±0.12	0.685±0.16
* Plus-minus values are means ± SD.			

Bone Mineral Density Change

At 3 months, the bone density of the spine had increased by 4.07% in Group I (95% confidence interval, 2.03-6.11) and by 0.64% in Group II (95% confidence interval, -0.54-1.02). The bone density at the femoral neck increased by 2.54% in Group I (95% confidence interval, 1.73-3.22) and by 0.80% in Group II (95% confidence interval, -0.32-1.13). The bone density of the total hip increased by 3.37% in Group I (95% confidence interval, 2.34-3.98) and decreased by 0.58% in Group II (95 percent confidence interval, -1.24-0.25).

Analyses showed there was significant difference between Group I and Group II in BMD percentage change. The difference between the changes in the two groups was 3.43% for the change at the spine (95% confidence interval, 1.37-4.94; P=0.01), 1.74% for the change at the femoral neck (95 percent confidence interval, 0.34 to 3.36; P=0.04), and 3.95% for the change at the total hip (95 percent confidence interval, 1.02 to 4.71; P=0.03).

At 12 months, the BMD of the spine had increased by 5.66% in Group I (95% confidence interval, 2.12-7.23) and decreased by 0.51% in Group II (95% confidence interval, -0.54-1.02). The bone density at the femoral neck increased by 3.49% in Group I (95% confidence interval, 1.73-5.22) and by 0.03% in Group II (95% confidence interval, -0.62-0.93). The bone density of the total hip increased by 4.11% in Group I (95% confidence interval, 2.34-5.98) and decreased by 0.07% in Group II (95 percent confidence interval, -1.01-0.98).

Difference between Group I and Group II in BMD percentage change is significant at 12 months. The difference between the changes in the two groups was 6.17% for the change at the spine (95% confidence interval, 4.02-8.94; P=0.003), 3.46% for the change at the femoral neck (95 percent confidence interval, 1.27 to 5.14; P=0.02), and 4.18% for the change at the total hip (95 percent confidence interval, 2.23 to 6.57; P=0.01).

Table 2. Change in BMD at 3 Months

BMD (g/cm^2)	Group I			Group II			Group III		
	Base	**3 mo**	**%Chg**	**Base**	**3 mo**	**%Chg**	**Base**	**3 mo**	**%Chg**
Lumbar Spine (L1-L4)	0.778 ±0.16	0.811 ±0.19	4.07	0.785 ±0.15	0.790 ±0.16	0.64	0.797 ±0.17	0.795 ±0.14	-0.25
Left Femoral Neck	0.631 ±0.12	0.647 ±0.14	2.54	0.628 ±0.14	0.633 ±0.12	0.80	0.637 ±0.15	0.640 ±0.12	0.27
Total Hip	0.682 ±0.17	0.705 ±0.17	3.37	0.693 ±0.12	0.689 ±0.17	-0.58	0.685 ±0.16	0.680 ±0.13	0.03
* Plus-minus values are means ± SD.									

Table 3. Change in BMD at 12 Months

BMD (g/cm^2)	Group I			Group II			Group III		
	Base	**12 mo**	**%Chg**	**Base**	**12 mo**	**%Chg**	**Base**	**12 mo**	**%Chg**
Lumbar Spine (L1-L4)	0.778 ±0.16	0.822 ±0.18	5.66	0.785 ±0.15	0.781 ±0.13	-0.51	0.797 ±0.17	0.791 ±0.17	-0.75
Left Femoral Neck	0.631 ±0.12	0.653 ±0.16	3.49	0.628 ±0.14	0.630 ±0.17	0.03	0.637 ±0.15	0.634 ±0.15	-0.47
Total Hip	0.682 ±0.17	0.710 ±0.20	4.11	0.693 ±0.12	0.688 ±0.21	-0.07	0.685 ±0.16	0.677 ±0.16	-1.17
* Plus-minus values are means ± SD.									

Secondary analyses revealed that the difference in BMD change in the spine is significant between Group I and Group III (6.41%; 95 percent confidence interval, 4.03-8.12; P=0.001). But there was no significant difference between Group II and Group III (0.25%; 95 percent confidence interval, –1.05 to 1.16; P=0.35). For the femoral neck, the estimated difference between Group I and Group III was 3.96% (95 percent confidence interval, 2.10 to 6.73; P=0.003), and the estimated difference between Group II and Group III was 0.50% (95 percent confidence interval, -0.91 to 1.06; P=0.05). For the total hip, the estimated difference between Group I and Group III was 5.28% (95 percent confidence interval, 3.48 to 7.31; P=0.001), and the estimated difference between Group II and Group III was 1.24% (95 percent confidence interval, -0.13-2.56; P=0.04).

BMD changes by age in Group I at 3 months and 12 months are reported in Table 4 and Table 5 respectively. Figure 2 shows that the estimated BMD percentage increase declines by age. This phenomenon is consistent at 3 months and 12 months.

Table 4. CalAA: Change in BMD at 3 Months By Age Groups

Age Group		Lumbar Spine (L1-L4) (g/cm^2)	Left Femoral Neck (g/cm^2)	Total Hip (g/cm^2)
45-49	Baseline	0.792±0.16	0.653±0.12	0.702±0.17
	3 months	0.864±0.22	0.695±0.16	0.748±0.21
	%Change	9.09	6.04	6.55
50-54	Baseline	0.788±0.17	0.647±0.11	0.695±0.16
	3 months	0.850±0.21	0.674±0.15	0.725±0.12
	%Change	7.87	4.17	4.32
55-59	Baseline	0.782±0.18	0.638±0.13	0.687±0.15
	3 months	0.839±0.21	0.660±0.12	0.711±0.17
	%Change	7.29	3.45	3.49
60-64	Baseline	0.776±0.15	0.633±0.14	0.680±0.13
	3 months	0.822±0.19	0.650±0.15	0.699±0.17
	%Change	5.93	2.69	2.79
65-69	Baseline	0.773±0.16	0.627±0.12	0.675±0.17
	3 months	0.816±0.18	0.641±0.16	0.690±0.23
	%Change	5.56	2.18	2.22
70-74	Baseline	0.764±0.14	0.623±0.15	0.668±0.13
	3 months	0.800±0.17	0.633±0.18	0.679±0.15
	%Change	4.71	1.61	1.65
75-79	Baseline	0.762±0.18	0.621±0.12	0.663±0.16
	3 months	0.794±0.22	0.627±0.16	0.671±0.19
	%Change	4.20	0.97	1.21
80-84	Baseline	0.734±0.19	0.602±0.15	0.645±0.14
	3 months	0.764±0.21	0.605±0.16	0.647±0.17
	%Change	4.09	0.50	0.31
Over 84	Baseline	0.703±0.21	0.586±0.19	0.613±0.24
	3 months	0.730±0.17	0.589±0.16	0.617±0.18
	%Change	3.84	0.51	0.65

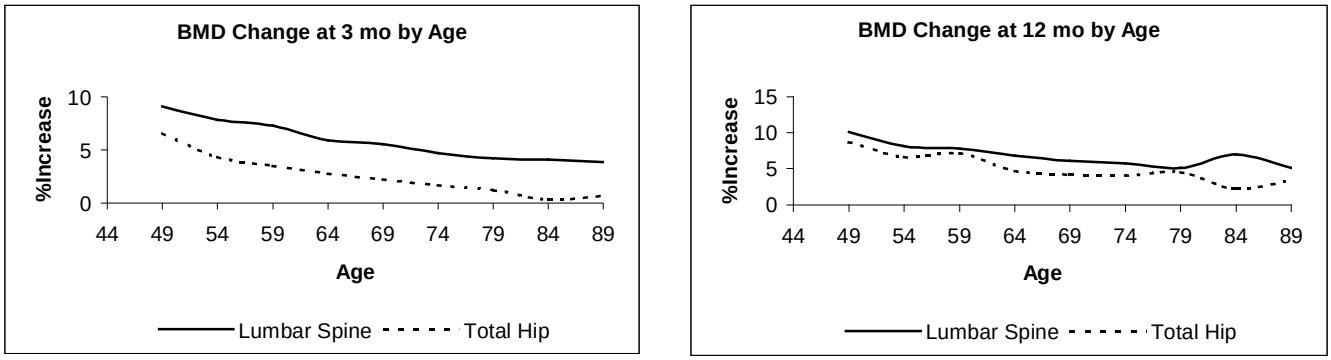
* Plus-minus values are means ± SD.

Table 4. CalAA: Change in BMD at 12 Months By Age Groups

Age Group		Lumbar Spine (L1-L4) (g/cm^2)	Left Femoral Neck (g/cm^2)	Total Hip (g/cm^2)
45-49	Baseline	0.792±0.16	0.653±0.12	0.702±0.17
	12 months	0.872±0.21	0.703±0.13	0.763±0.24
	%Change	10.10	7.66	8.69
50-54	Baseline	0.788±0.17	0.647±0.11	0.695±0.16
	12 months	0.852±0.15	0.691±0.18	0.741±0.15
	%Change	8.12	6.80	6.62
55-59	Baseline	0.782±0.18	0.638±0.13	0.687±0.15
	12 months	0.843±0.19	0.683±0.17	0.736±0.19
	%Change	7.80	7.05	7.13
60-64	Baseline	0.776±0.15	0.633±0.14	0.680±0.13
	12 months	0.829±0.13	0.672±0.16	0.712±0.13
	%Change	6.83	6.16	4.71
65-69	Baseline	0.773±0.16	0.627±0.12	0.675±0.17
	12 months	0.820±0.21	0.664±0.14	0.703±0.21
	%Change	6.08	5.90	4.15
70-74	Baseline	0.764±0.14	0.623±0.15	0.668±0.13
	12 months	0.808±0.22	0.656±0.13	0.695±0.17
	%Change	5.76	5.30	4.04
75-79	Baseline	0.762±0.18	0.621±0.12	0.663±0.16
	12 months	0.801±0.20	0.644±0.13	0.693±0.17
	%Change	5.12	3.70	4.52
80-84	Baseline	0.734±0.19	0.602±0.15	0.645±0.14
	12 months	0.785±0.25	0.621±0.19	0.659±0.21
	%Change	6.95	3.16	2.17
Over 84	Baseline	0.703±0.21	0.586±0.19	0.613±0.24
	12 months	0.739±0.18	0.603±0.21	0.634±0.22
	%Change	5.12	2.90	3.43

* Plus-minus values are means ± SD.

Figure 2. CalAA: BMD Change by Age



Conclusion

We conclude that calcium aspartate anhydrous increases bone mineral density significantly in 3-12 months. Calcium citrate plus vitamin D may help slow down bone loss at the hip.

References

1. Valimaki MJ, Kinnunen K, Tahtela R, et al. A prospective study of bone loss and turnover after cardiac transplantation: effect of calcium supplementation with or without calcitonin. Osteoporos Int 1999;10:128-136.
2. Wu CY, Li J, Jergas M, Genant HK. Comparison of semiquantitative and quantitative techniques for the assessment of prevalent and incident vertebral fractures. Osteoporos Int 1995;5:354-370.
3. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 1994;4:368-381.
4. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292-299.
5. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis: a comparison of calcium, calcitriol, and calcitonin. N Engl J Med 1993;328:1747-1752.
6. Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. J Bone Miner Res 1996;11:984-996.
7. Luengo M, Picado C, Rio LD, Guañabens N, Montserrat JM, Setoain J. Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study. Thorax 1991;46:803–6.
8. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
9. Reid IR, Ibbertson HK. Evidence for decreased tubular reabsorption of calcium in glucocorticoid-treated asthmatics. Horm Res 1987;27:200–4.
10. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. Osteoporosis Int 1997;7:390–406.
11. Raef H, Frayha HH, El-Shaker M, Al-Humaidan A, Conca W, Sieck U, Okane J; Osteoporosis Working Group. Recommendations for the diagnosis and management of osteoporosis: a local perspective.
12. Ann Saudi Med. 2004 Jul-Aug;24(4):242-52.
13. Ettinger MP. When and how to use dual energy X-ray absorptiometry in diagnosis and treatment of osteoporosis. J Fla Med Assoc. 1995 May;82(5):352-7.
14. Inoue T, Yamazaki K, Kushida K. Utility of dual X-ray absorptiometry and single X-ray absorptiometry as diagnostic tools for involutional osteoporosis. Osteoporos Int. 1997;7 Suppl 3:S117-9.

15. Kanis JA, Devogelaer JP, Gennari C. Practical guide for the use of bone mineral measurements in the assessment of treatment of osteoporosis: a position paper of the European foundation for osteoporosis and bone disease. The Scientific Advisory Board and the Board of National Societies. Osteoporos Int. 1996;6(3):256-61.
16. Yu W. Diagnosis of osteoporosis and some related issues. Zhonghua Yi Xue Za Zhi. 2005 Mar 23;85(11):725-7. Chinese.
17. Dambacher MA, Haas HG, Ruegsegger P. Pathophysiology of osteoporosis and bone density determination. Internist (Berl). 1991 Feb;32(2):63-9. German.
18. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int. 2000;11(3):192-202.
19. Prestwood KM, Kenny AM. Osteoporosis: pathogenesis, diagnosis, and treatment in older adults. Clin Geriatr Med. 1998 Aug;14(3):577-99.
20. Rubin CD. Treatment considerations in the management of age-related osteoporosis. Am J Med Sci. 1999 Sep;318(3):158-70.
21. Sartoris D, Dalinka MK, Alazraki N, Berquist TH, Daffner RH, DeSmet AA, el-Khoury GY, Goergen TG, Keats TE, Manaster BJ, Newberg A, Pavlov H, Schweitzer ME, Haralson RH 3rd, McCabe JB. Osteoporosis and bone-mass measurement. American College of Radiology. ACR Appropriateness Criteria. Radiology. 2000 Jun;215 Suppl:397-414.
22. Ishikawa K, Ohta T, Hirano M, Yoshimoto K, Tanaka S, Inoue S. Relation of lifestyle factors to metacarpal bone mineral density was different depending on menstrual condition and years since menopause in Japanese women. Eur J Clin Nutr. 2000 Jan;54(1):9-13.
23. Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, Sarkar S, Liu T, Wong M, Draper MW. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group. Osteoporos Int. 1999;10(4):330-6. Erratum in: Osteoporos Int 1999;10(5):433.
24. Ensrud KE, Duong T, Cauley JA, Heaney RP, Wolf RL, Harris E, Cummings SR. Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake. Study of Osteoporotic Fractures Research Group. Ann Intern Med. 2000 Mar 7;132(5):345-53.
25. Jiang Y, Zhao J, Rosen C, Geusens P, Genant HK. Perspectives on bone mechanical properties and adaptive response to mechanical challenge. J Clin Densitom. 1999 Winter;2(4):423-33.
26. Wu H, Deng X, Wang Y. Relationship between osteoporosis and metabolism of calcium and bone. Hunan Yi Ke Da Xue Xue Bao. 1998;23(3):261-4. Chinese.
27. Bohic S, Rey C, Legrand A, Sfihi H, Rohanizadeh R, Martel C, Barbier A, Daculsi G. Characterization of the trabecular rat bone mineral: effect of ovariectomy and bisphosphonate treatment. Bone. 2000 Apr;26(4):341-8.
28. Ongphiphadhanakul B, Piaseu N, Tung SS, Chailurkit L, Rajatanavin R. Prevention of postmenopausal bone loss by low and conventional doses of calcitriol or conjugated equine estrogen. Maturitas. 2000 Feb 15;34(2):179-84.
29. Filipponi P, Cristallini S, Policani G, Schifini MF, Casciari C, Garinei P. Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. Bone. 2000 Mar;26(3):269-74.