Comparing the Effect of Short Term Post Meals and Bedtime Calcium Supplementation on the C-terminal Telopeptide Crosslinks and PTH Levels in Postmenopausal Osteopenic Women

Somlak Chuengsamarn, MD*,
Sompongse Suwanwalaikorn, MD**

** Department of Medicine, Faculty of Medicine, Srinakharinwirot University*
*** Department of Medicine, Faculty of Medicine, Chulalongkorn University*

Background: *Calcium supplement for postmenopausal osteopenic women can significantly reduce bone loss and the risk of fractures. However, the optimal time for calcium supplementation remains controversial.*
Objective: *The aim of the present study was to compare the effect of twice daily post meals and bedtime calcium supplementation for a two week periods, on C-terminal telopeptide crosslinks and PTH levels in postmenopausal osteopenic women.*
Design: *A randomized double blind placebo-control, crossover design, was carried out on 3 consecutive periods 3 of a 2-week treatment regimen. In the first period, all the subjects randomly received either two calcium carbonate tablets (Chalk Cap® all subjects randomly received either two calcium 334 mg per tab) or placebo at bedtime with one tablet of calcium tablet or placebo after breakfast and dinner for two weeks. In the second period, subjects received only placebo tablets after the meals and at bedtime for 2 weeks. In the third period subjects received either calcium carbonate or placebo for another two weeks. The C-terminal telopeptide crosslinks were measured at 8.00 am and serum PTH were sampled at 8 time points (12.00 am, 2.00 am, 4.00 am, 6.00 am, 8.00 am, 9.00 am, 5.00 pm, and 7.00 pm respectively by the end of each study at the first and third period.*
Results: *The present study showed thirty-six postmenopausal subjects (mean age 63.9 $\pm$ 3.66 years) participated in the present study. The mean T-score BMD of the spine and hip were -2.96 $\pm$ 0.87 and -2.96 $\pm$ 0.77 gm/cm^2. C-terminal telopeptide crosslinks levels of the bedtime supplementation were significantly lower than the post meal supplementation (0.228 $\pm$ 0.002 ng/ml vs 0.313 $\pm$ 0.003 ng/ml, $p < 0.001$). The mean night time serum PTH level during the bedtime was significantly lower than the post meal period. (25.17 $\pm$ 2.31 pg/ml vs 31.930 $\pm$ 2.677 pg/ml, $p < 0.001$). No differences in the post meal PTH level between two periods were observed.*
Conclusion: *The bedtime calcium supplementation appeared to reduce the bone resorption marker and night time serum PTH levels greater than the post meal calcium supplementation in this short term period study. However, long term comparison may be needed.*

Keywords: *Parathyroid hormone, Bone marker, Osteopenic women, Calcium intake*

J Med A ssoc Thai 2005; 88(Suppl 1): S12-20
Full text. e-Journal: *http://www.medassocthai.org/journal*

Correspondence to : Chuengsamarn S, Division of Endocrinology, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Maha Chakri Sirinthorn Medical Center, Nakhon-Nayok 26120, Thailand. Phone: 0-3739-5085-6 ext 11001, Fax: 0-3439-5085 ext 11003, E-mail: somlukc@swu.ac.th

Postmenopausal women have increased risks of osteoporosis and estrogen rate especially 15 years after menopause because of the reducing and increasing of PTH in the aging. A recent study by meta analysis of calcium supplementation for the prevention of postmenopausal osteoporosis[1] showed that calcium supplementation for at least 2-years had prevented bone loss and increased BMD of the spine at significant statistic(mean difference 1.66, 95%CI 0.92-2.39, $p < 0.01$). Some randomized control trials[2-5] showed the benefit of calcium plus vitamin D supplementation in the elderly for prevention of bone loss and reduction of fracture rates. A recommendation of the 1994 NIH Consensus Development Conference[6] suggested that for postmenopausal osteoporosis optimal doses of calcium (1,500 mg/D) should be taken.

Bendich et al[7] supported the benefit of calcium supplementation (1,200 mg/D) in postmenopausal women for prevention of hip fracture. The present study showed the data of cost effectiveness in the treatment group had more benefit than placebo group. Heller et al[8] showed that calcium citrate was more absorbable than the calcium carbonate but further study[9-12] showed no difference of calcium absorption in statistics between the two formulas. Heany RP[13] showed that the nocturnal PTH in postmenopausal women had more increased levels than premenopausal women and further more many studies[14,15] supported that nocturnal calcium supplementation could reduce PTH and bone resorption.

Nowadays, calcium supplementation was taken post meals because the acidity is increased in calcium absorption. However, the optimal time of calcium supplementation between nocturnal and post meals group for reduction of PTH and bone resorption was not known. Here, the authors presented detailed analysis of the optimal time of calcium supplementation in postmenopausal osteopenic women. A double-blind, randomized, crossover study was performed to compare the effect of twice daily post meals and bedtime calcium supplementation for a two week period, on C-terminal telopeptide crosslinks and PTH levels in 36 patients with postmenopausal osteopenic.

Material and Method

The study was performed and collected data from October, 2002 to April, 2003. Thirty-eight women aged 60-70 yr. with osteopenic were recruited at the King Chulalongkorn Memorial Hospital, Endocrinology division. All subjects were healthy, had no disease known to affect bone or mineral metabolism, and were not taking any medication which affected in bone metabolism. The subjects had T-Score BMD performed at spine and hip in range (-2.0 to -3.0 gm/cm^2) by Dual-energy x-ray absorptiometry (Dexa scan). Table1 shows the biochemical characteristics of the thirty-eight subjects. Two subjects had not participated during this project because of acute asthmatic attack and acute ischemic heart disease. They were not affected by adverse effect of calcium supplementation. The study was approved by the local ethical committee of the King Chulalongkorn Memorial Hospital center, and all subjects gave written informed consent.

Study design

A randomized double blind placebo-control, crossover design, was carried on 3 consecutive periods of 2-week treatment regimen. The first period, all subjects randomly received either two calcium carbonate tablets (Chalk Cap® 835 mg = elemental calcium 334 mg per tab) or placebo at bedtime with one tablet of calcium tablet or placebo after breakfast and dinner for two weeks. The second period, the subjects received only placebo tablet after the meals and bedtime for 2 weeks. The third period, the subjects received either calcium carbonate or placebo for another two weeks. The Fig. 1 showed three periods of the project.

All subjects were hospitalized at the end of the first and third period for 24 hours for the measurement of PTH and C-terminal telopeptide crosslink (CTx). The subjects received standardized meals, served at 08.00, 12.00, 18.00 hr on study day 14 and 12, each subject was continued to take the same calcium protocol and blood samples were collected, withdrawn through an indwelling venous catheter placed in the forearm, for the measurement of PTH levels at 8 points time (12.00 am, 2.00 am, 4.00 am, 6.00 am, 8.00 am, 9.00 am, 5.00 pm, 7.00 pm) and CTx level at 8.00 am after overnight footing. Safety assessment included vital signs (pulse rate, blood pressure, and temperature); electrocardio-grams; biochemistry; hematology; and urinalysis.

Laboratory method

Serum was separated from blood and serum and urine samples ware stored at -20^{0}C until analyzed. All samples from the same person were analyzed in

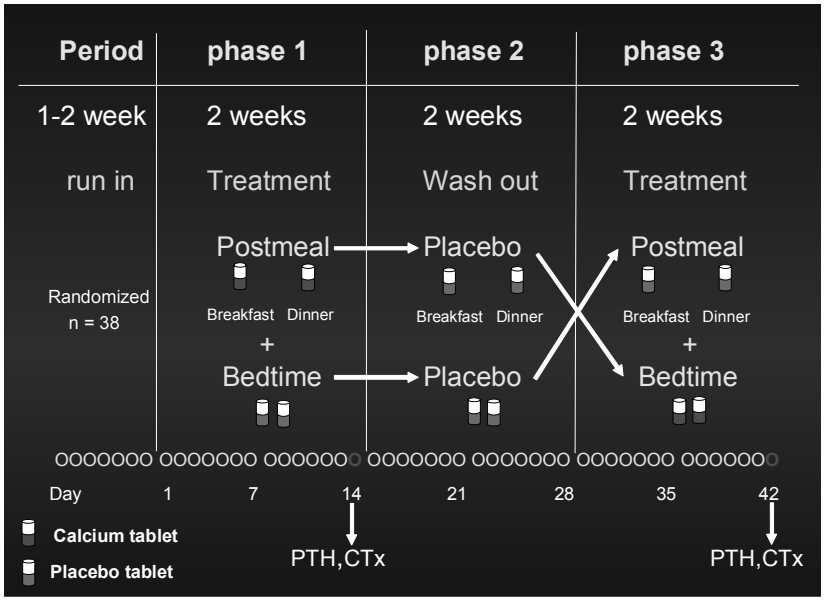

Fig. 1 Designs of Studies were divided into three periods. Arrows indicate the time at the end of the first and third period (Day 14 and Day 42) when each subject was hospitalized for measurement of PTH levels at 8 points in time (12.00 am, 2.00 am, 4.00 am, 6.00 am, 8.00 am, 9.00 am, 5.00 pm, 7.00 pm) and S-CTx at 8.00 am after overnight fasting

the same assay in a randomized order. Serum intact PTH concentrations (pg/ml) were measured with automatic electrochemiluminescence immunoassay system [Roche Diagnostic (Elecsys 2010/intact PTH)]. The intra and inter assay coefficients of variation of PTH were 3-4% and 3-5% respectively. Serum C-terminal telopeptide crosslinks (S-CTx) concentrations (ng/ml) also were measured with automatic electrochemiluminescence immunoassay system [Roche Diagnostic (Elecsys 2010/b-CrossLaps serum)]. The intra and inter assay coefficients of variation of S-CTx were 4-6% and 5-8% respectively. Serum total calcium, serum phosphate, urinary calcium and urinary creatinine concentrations were measured by using routine laboratory methods, and the CVs were between 1.5% and 2.5%

Statistical analysis

The assumption of normality of all data was investigated by use of a Kolmogorov-Smirnov test, in which the null hypothesis that the data represented a random sample from the normal distribution was tested. When this hypothesis was not rejected, a paired studentís t test was used for assessing the statistical significance, compared with the control. The Wilcoxonís signed rank test, a nonparametric analog to the paired t test, was used when data did not represent a random sample from normal distribution. Correlation analysis was performed by the use of Spearmanís rank correlation test and the one-way ANOVA was used. When significant overall effects were obtained by this method, comparisons were made using MC. Nema X^2 multiple comparisons test. Data are expressed as mean $\pm$ SEM. $P < 0.05$ was considered significant.

Results

Thirty-eight women were mean age 63.84 $\pm$ 3.62 yr. and range of age (60-70yr). They had mean time of postmenopausal 17 $\pm$ 4.1 yr and range of time (9-27 yr) their mean BMD of hip and vertebral were -2.87 $\pm$ 0.75 gm/cm^2 and -2.78 $\pm$ 0.86 gm/cm^2 respectively. The ranges of BMD hip and vertebral were -4.80 to -1.40 gm/cm^2 and -4.70 to -1.30 gm/cm^2 respectively. Screening biochemical laboratories. (Serum calcium, serum phosphorous, serum creatinine) were normal limit. Table 1 shows the general characteristics of the thirty-eight women.

Primary outcomes of the present study purposed to compare the effect of twice daily post meals and bedtime calcium supplementation on the C-terminal telopeptide crosslinks (S-CTx) and PTH levels in postmenopausal osteopenic women. Table 2 shows all data of PTH and S-CTx levels.

Table 1. Baseline patients characteristics (n = 38)

	Mean ± SD	Range
Population characteristics		
Age (yr)	63.84 ± 3.62	60-70
Time since menopause (yr)	17 ± 4.1	9 - 25
Height (m)	1.65 ± 0.08	1.54 - 1.82
Weight (kg)	58.89 ± 8.48	47.0 - 75.0
BMI (kg/m^2)	21.55 ± 2.32	15.45 - 26.45
BMD (g/cm^2)		
Total Hip	-2.87 ± 0.75	(-4.80) - (-1.40)
Lumbar Spine (L_1-L_4)	-2.78 ± 0.86	(-4.70) - (-1.30)
Biochemical markers		
Serum calcium (mg/dl)	8.74 ± 0.40	8.10 - 9.60
Serum phosphorus (mg/dl)	3.46 ± 0.44	2.80 - 4.20
Serum creatinine (mg/dl)	0.56 ± 0.31	0.10 - 1.30

Thirty-six subjects were showed PTH levels at 8 points time (12.00 am, 2.00 am, 4.00 am, 6.00 am, 8.00 am, 9.00 am, 5.00 pm, and 7.00 pm) and S-CTx levels at 8.00 am after an overnight fasting. These data were classified to 2 groups which included a post meals group and bedtime group after crossover of each subject at the end of the project. Thirty-six PTH levels were presented as mean ± SE and range by 8 points time (12.00 am, 2.00 am, 4.00 am, 6.00 am, 8.00 am, 9.00 am, 5.00 pm, and 7.00 pm). Thirty-six serum CTx levels were also presented as mean ± SE and range at 8.00 am. The comparing of mean PTH and S-CTx levels between post meal and bedtime group used statistic of paired t-test and 95%CI (upper/lower limit) was showed significantly at $p < 0.05$.

Mean PTH levels at each point time (12.00 am, 2.00 am, 4.00 am and 8.00 am) were compared between post meal and bedtime group by 95%CI of paired t-test (5.99-11.75, 3.05-11.14, 2.97-12.52, 1.01-8.36) which were significantly at $p < 0.001$, $p = 0.001$, $p = 0.002$ and $p = 0.014$ respectively. The comparison mean S-CTx levels at 8.00 am of post meal and bedtime group by using 95%CI of paired t-test was significant at $p < 0.001$ (Table 2).

Bar graphs (Fig.2) are showed comparing the mean S-CTx levels (n = 36) between post meals and bedtime group at 8.00 am after an overnight fasting. Mean S-CTx levels of post meals group was 0.313 ± 0.027 (0.046-0.816) and bedtime group was 0.227 ± 0.025 (0.010-0617). Mean S-CTx levels of the bedtime group was lower than the post meals group at statistical significance ($p < 0.001$) and 95%CI (0.06-0.11).

Bar graphs (Fig.3) are showed comparing the mean PTH levels (n = 36) between post meals and bedtime group at 8 points time (12.00 am, 2.00 am, 4.00 am, 6.00 am, 9.00 am, 5.00 pm and 7.00 pm). Mean PTH levels at 8 points time of the post meals group were 29.99 ± 2.39, 30.77 ± 2.96, 33.38 ± 3.07, 33.57 ± 2.79, 33.29 ± 2.52, 34.73 ± 2.81, 37.46 ± 3.37 and the bedtime group were 21.12 ± 1.99, 23.68 ± 2.21, 25.64 ± 2.49, 30.26 ± 2.82, 28.60 ± 2.46, 30.88 ± 2.39, 35.83 ± 2.81 and 39.71 ± 3.31. Mean PTH levels at each time (12.00 am, 2.00 am, 4.00 am and 8.00 am) of the bedtime group was lower than the post meals group at significantly statistic ($p < 0.001$, $p = 0.001$, $p = 0.002$ and $p = 0.014$) and 95%CI (5.99-11.75, 3.05-11.14. 2.97-12.52 and 1.01-8.36).

Secondary outcomes of the present study showed adverse effects of calcium supplementation between twice daily post meals group and bedtime group and all adverse events (AEs) showed as frequency rates (%). Percentage of adverse events (n = 38) was classified to 2 groups (twice daily post meals group and bedtime group) as shown in Table 3. Any adverse events (related or non-related drug) of the post meals group were 3 events (7.5%) and the bedtime group was 2 events (5%). Drug-related adverse events of the post meals group were 2 events (5%) and the bedtime group was 1 event (2.5%). Adverse events leading to withdrawal from this project were not related calcium supplementation and these events were acute asthmatic attack (post meals group) and acute ischemic heart disease (bedtime group).

Table 2. Mean of serum PTH and C-terminal telopeptide crosslinks levels comparing between twice daily post meals and bedtime calcium supplementation group (n = 36)

Point time	Calcium Supplementation				Paired t-test (1)		
	Twice daily Post meal group		Bedtime group		95% CI		P value
PTH levels	Mean ± SE	Range	Mean ± SE	Range	Lower	Upper	
12.00 am	29.99 ± 2.39	12.36 - 77.03	21.12 ± 1.99	6.69 - 70.50	5.99	11.75	p < 0.001
2.00 am	30.77 ± 2.96	12.55 - 97.24	23.68 ± 2.21	6.01 - 81.96	3.05	11.14	p = 0.001
4.00 am	33.38 ± 3.07	13.15 - 108.30	25.64 ± 2.49	8.62 - 89.68	2.97	12.52	p = 0.002
6.00 am	33.57 ± 2.79	14.67 - 95.67	30.26 ± 2.82	10.63 - 105.50	-0.73	7.37	p = 0.106
8.00 am	33.29 ± 2.52	15.05 - 93.98	28.60 ± 2.46	12.61 - 82.85	1.01	8.36	p = 0.014
9.00 am	34.73 ± 2.81	14.86 - 82.80	30.88 ± 2.39	11.93 - 82.73	-0.11	7.81	p = 0.056
5.00 pm	33.93 ± 2.97	13.35 - 100.80	35.83 ± 2.81	15.76 - 85.63	-5.64	1.84	p = 0.309
7.00 pm	37.46 ± 3.37	14.94 - 100.50	39.71 ± 3.31	12.48 - 104.60	-6.38	1.87	p = 0.275
CTx level							
8.00 am	0.313 ± 0.027	0.046 - 0.816	0.227 ± 0.025	0.010 - 0.617	0.06	0.11	p < 0.001

Data shown as mean±SE, Range
(1) To compare PTH levels/CTx level between twice daily post meal group and bedtime group

Table 3. Summary of adverse events (AEs) which were related to calcium or not related to calcium supplementation were compared between the twice daily post meals and the bedtime calcium supplementation group

	twice daily post meals gr n = 19	bedtime gr n = 19
Any AEs	3 (16%)	3 (16%)
Drug-related AEs	2 (10%)	1 (5%)
Serious AEs	0	0
Drug-related serious AEs	0	0
AEs leading to withdrawal	1 (5%)	1 (5%)
Drug-related AEs leading to withdrawal	0	0
Seriuos AEs leading to withdrawal	0	0
Drug-related seriuos AEs leading to withdrawal	0	0

Discussion

The amount of calcium over 1 gm can reduce PTH levels and increase serum calcium and urinary calcium, thus loading calcium may be reduced by either nocturnal or daily PTH[17,18]. However, and acidity increases calcium absorption although calcium supplementation was usually taken multiple post meals with low doses under 500 mg[19].

PTH levels were variable in daily and increased in the nocturnal time[20]. A study[21] supported evidence that bone resorption markers (CTx and NTx) also increased in the nocturnal time.

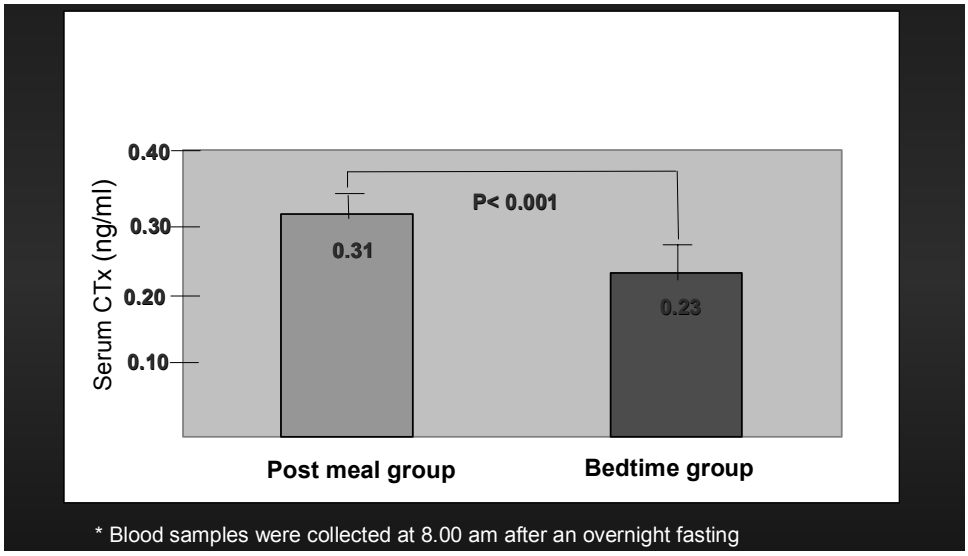

Fig. 2 Mean of serum CTx levels comparing the twice daily post meals and bedtime calcium supplementation group (n = 36)

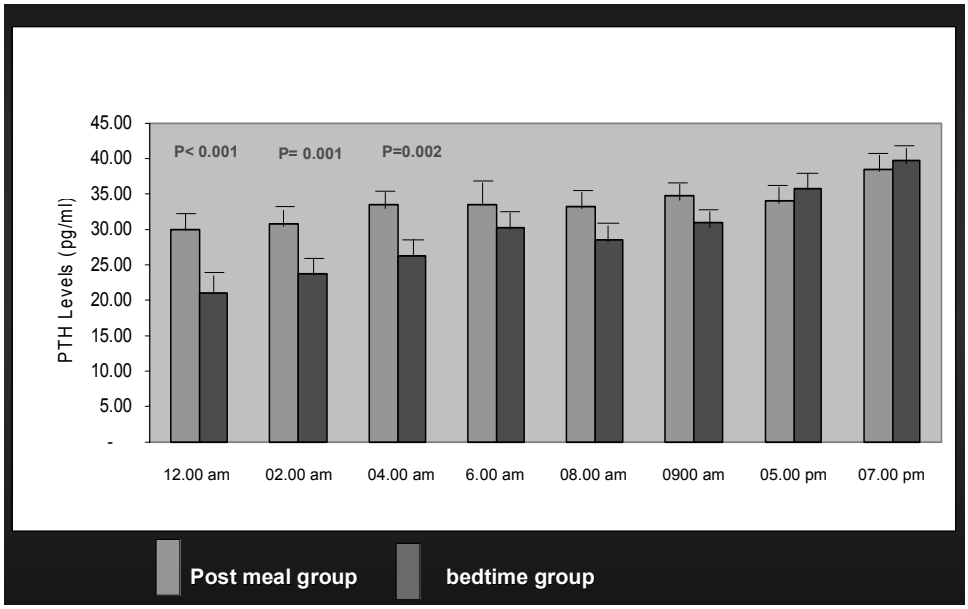

Fig. 3 Mean of serum PTH levels comparing the twice daily post meals and bedtime calcium supplementation group (n = 36)

Heany RP[13] suggested that the levels of nocturnal PTH in post menopausal women were higher than premenopausal women although an issue was debated that the nocturnal calcium supplementation may be reduced PTH and bone resorption markers more than the daily calcium supplementation. At the homeostasis of calcium absorption, amounts of calcium elemental between 1,000 mg and 2,000 mg showed no difference in reduction of PTH levels[22].

Addition to the evidence of Heany RP[23] supported that the nocturnal calcium supplementation could reduce both PTH and bone resorption markers. A recent study[23] showed the effect of calcium load in a single dose on the PTH and bone

resorption marker levels. The results were compared between nocturnal and morning calcium supplementation in the premenopausal women and showed no difference between the two groups. However, no randomized controlled trail was studied the effect of the short-term calcium supplementation comparing between twice daily post meals and bedtime groups in postmenopausal osteopenic Thai women, although the author purposed to study the effect of 2-week calcium supplementation in these populations for choosing the optimal time.

The authors presented the results that comparing the mean of PTH and S-CTx levels in thirty-six subjects between twice daily post meals and the bedtime calcium supplementation and also summarized that the bedtime calcium supplementation could reduce the mean of PTH and S-CTx levels more than the twice daily post meals calcium supplementation at statistical significance. The presented data showed that the adverse effects of the bedtime calcium supplementation no more than the twice daily post meals calcium supplementation although the authors concluded that the 2-week of the bedtime calcium supplementation could be more beneficial than the twice daily post meals calcium supplementation in postmenopausal osteopenic than women for prevention osteoporosis.

The present results were opposite to a previous study[23] that a single dose of calcium load compared between morning time (8.00 hr) and nocturnal time (23.00 hr) had no effected on reduction of PTH and bone markers (bone resorption and formation markers). Opposite to the present results, the authors may explain in many reasons between the present study and the previous study. The number subjects of the previous study were lower than the present study and their subjects were aimed in the premenopausal women (21-34 yr). Therefore, the PTH levels might not be increased higher than postmenopausal women (60-70 yr) in the present study. The second reason, the previous study used a single dose of calcium load whereas the present study used 2-week of calcium load. For this reason, the results of many studies[14,15,24] were also the same as the present study that their studies did not used a single dose of calcium load but they used at least 2-week of calcium load. Because of a single dose of calcium load may be not resulted in reduction of bone markers by suppressed PTH. The third reason, the previous study used calcium Sandoz formula (6,810 mg calcium lactate gluconate, 300 mg calcium carbonate, 1350 mg acid citrate anhydrous, and 40 mg aspartame) and four 250 mg doses of which these components might affect the maximum dose of PTH suppression. The final reason, the previous study used urinary total pyridinoline (U-T-Pyd) of which bone resorption markers were less sensitivity than other markers. For this reason, the results of many studies[14,15,25] were also the same as the present study which they used bone resorption markers (U-T-Dpd and U-F-Dpd) and their bone resorption markers were more sensitivity than the markers of the previous study. In addition to this, the present study used serum C-terminal telopeptide crosslink (S-CTx) as bone resorption marker of which the sensitivity was more than the markers the previous study. A recent study[26] compared the sensitivity of bone resorption markers (U-T-Pyd, U-T-Dpd, U-F-Dpd and CTx) after calcium load in postmenopausal women of which the results showed that CTx was the most sensitivity markers. Garnero[27] showed that serum CTx at 8.00 hr (after overnight footing) was a more sensitivity marker than urinary CTx (U-CTx), because U-CTx had affected by many factors such as renal function, collection of urinary volume and daily diets.

In conclusion, the present data suggested that the 2-weeks of the bedtime calcium supplementation could reduce both S-CTx and PTH levels more than the twice daily meals calcium supplementation. No serious side effects occurred during calcium supplementation and their side effects of the bedtime calcium supplementation were not more than the twice daily post meals calcium supplementation. Further studies will also address the question of whether its comparison trial to confirm its efficacy and safety.

References

1. Shea B, Wells G, Cranney A. Meta-analysis of calcium supplementation for the prevention of Postmenopausal Osteoporosis. End Rev 2002; 23: 552-9.
2. Chapuy MC, Arlot ME, Duboeuf F. Vitamin D3 and calcium to prevent hip fractures in the elderly woman. N Engl J Med 1992; 327: 1637-42.
3. Chevalley T, Rizzoli R, Nydegger V. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 1994; 4: 254-2.

4. Recker RR, Hinders S, Davies KM. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 1996; 11: 1961-6.
5. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337: 670-6.
6. NIH Consensus Conference. Optimal calcium intake. JAMA 1994; 272: 1942-8.
7. Bendich A, Leader S, Muhuri P. Supplemental calcium for the prevention of hip fracture: potential health-economic benefits. Clin Ther 1999; 21: 1058-72.
8. Heller HJ, Stewart A, Haynes S, Pak CYC. Pharmacokinetics of calcium absorption from two commercial calcium supplements. J Clin Pharmacol 1999; 39: 1151-4.
9. Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 1999; 9: 19-23.
10. Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Gastrointestinal absorption of calcium from milk and calcium salts. N EngI J Med 1987; 317: 532-6.
11. Recker RR. Calcium absorption and achlorhydria. N EngI J Med 1985; 313: 70-3.
12. Heaney RP, Dowell SD, Bierman J. Absorbability and cost effectiveness in calcium supplementation. J Ann Coll Nutr 2001; 20: 239-46.
13. Heaney RP, Recker RR, Saville PD. Calcium balance and calcium requirements in middle-aged women. Am J Clin Nutr 1977; 43: 1603-11.
14. McKane WR, Khosha S, Egan KS. Role of parathyroid hormone in mediation nocturnal and age-related increase in bone resorption. J Clin Endrocrinol Metab 1996; 81: 1699-703.
15. Ledger GA, Burritt MF, Rao PC. Role of parathyroid hormone in mediating nocturnal and age-related increase in bone resorption. J Clin Endrocrinol Metab 1995; 80: 3304-10.
16. Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparation. Aust N Z J Med 1986; 16: 193-7.
17. Herfarth K, Drechsler S. Imhoff W. Calcium regulation hormones after oral and intravenous calcium administration. Eur J Clin Chem Clin Biochem 1992; 37: 511-9.
18. Horowiz M, Wishart JM. Goh D, Morris HA, Need AG, Nordin BEC. Oral calcium suppresses biochemical markers of bone resorption in normal men. Am J Clin Nutr 1994; 60: 965-8.
19. Liu CC, Kalu DN. Human parathyroid hormone (1-34) prevents bone loss and augments bone formation in sexually mature ovaricetomized rats. J Bone Miner Res 1990; 5: 973-82.
20. Herfarth K, Schmidt-Gayk H, Graf S, Maier A. Circadian rhythm and pulsatility of parathyroid hormone secretion in man. Clin Endocrinol 1992; 37: 511-9.
21. Hassager C, Risteli J, Risteli L, Jensen SB, Christiansen C. Diurnal variation in serum markers of type I collagen synthesis and degradation in healthy premenopausal women. J Bone Miner Res 1992; 7: 1307-11.
22. Johnson JA, Kumar R. Renal and intestinal calcium transport: roles of vitamin D and vitamin D-dependent calcium binding proteins. Semin Nephrol 1994; 14: 119-28.
23. Merja UM K‰rkk‰inen, Christel JE Lamberg-Allardt, Suvi Ahonen. Does it make difference how and when you take your calcium? The acute effects calcium on calcium and bone metabolism. Am J Clin Nutr 2001; 74: 335-42.
24. Zikan V, Haas T, Stepan IJ. Acute effects in healthy women of oral calcium on the calcium-parathyroid and bone resorption as assessed by serum beta-CrossLabs. Calcif Tissue Int 2001; 68: 352-7.
25. Rubinacci A, Melzi R, Zampino M. Total and free deoxypyridinoline after acute osteoclast activity inhibition. Clin Chem 1999; 45: 1510-6.
26. Kamel S, Fardellone P, Meddah B. Response of several markers of bone collagen degradation to calcium supplementation in postmenopausal women with low calcium intake. Clin Chem 1998; 44: 1437-42.
27. Garneo P. Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis. Clin Chem 2001; 47: 694-702.

การศึกษาเปรียบเทียบประสิทธิผลระหว่างการรับประทานแคลเซี่ยมเสริมหลังอาหาร 2 มื้อ และก่อนนอน ต่อการเปลี่ยนแปลงของระดับ ซีเทอร์มินอลเทโลเปปไทด์ครอสลิงค์ และพาราธัยรอยด์ฮอร์โมนในหญิง วัยหมดประจำเดือนที่มีกระดูกบาง

สมลักษณ์ จึงสมาน, สมพงษ์ สุวรรณวลัยกร

ที่มา: *การให้แคลเซี่ยมเสริมในหญิงวัยหมดประจำเดือนที่มีกระดูกบาง สามารถลดการลดลงของมวลกระดูก อัตราการหักของกระดูก อย่างไรก็ตามช่วงเวลาที่เหมาะสมในการรับประทานแคลเซี่ยมเสริม เพื่อให้ได้ประสิทธิภาพยังไม่มีข้อตกลงที่ชัดเจน*

วัตถุประสงค์ *: เพื่อศึกษาเปรียบเทียบประสิทธิผลในการรับประทานแคลเซี่ยมเสริมระหว่างการรับประทานหลัง อาหาร 2 มื้อ และก่อนนอน โดยวัดการเปลี่ยนแปลงของระดับซีเทอร์มินอลเทโลเปปไทด์ครอสลิงซ์ และพาราธัยรอยด์ฮอร์โมนในหญิงวัยหมดประจำเดือนที่มีกระดูกบาง*

วัสดุและวิธีการ: *การศึกษาแบบ Randomized double blind placebo - Control, cross over โดยแบ่งช่วงการศึกษาเป็น 3 ช่วงใช้เวลาช่วงละ 2 สัปดาห์ช่วงแรกของการศึกษาผู้ร่วมโครงการจะถูกสุ่มออกเป็น 2 กลุ่ม เพื่อรับประทานแคลเซี่ยมเสริม 1 เม็ดหลังอาหาร 2 มื้อ หรือ 2 เม็ด ก่อนนอน ช่วงที่สอง ผู้ร่วมโครงการทั้ง 2 กลุ่ม จะได้รับยาหลอกตลอดช่วงการศึกษา ช่วงที่สามผู้ร่วมโครงการทั้ง 2 กลุ่มจะได้รับยาแคลเซี่ยมตรงข้ามกับช่วงแรก โดยกลุ่มที่เคยได้รับแคลเซี่ยมหลังอาหารจะได้รับก่อนนอนแทน และกลุ่มที่ได้รับก่อนนอนจะได้รับหลังอาหารแทน เมื่อสิ้นสุดการวิจัยในช่วงที่ 1 และ 3 จะวัดระดับซีเทอร์มินอลเทโลเปปไทด์ ที่เวลา 8.00 น. และพาราธัยรอยด์ฮอร์โมนที่เวลา 24.00 น., 2.00 น., 6.00 น., 8.00 น., 9.00 น., 17.00 น., 19.00 น.*

ผลการศึกษา: *ผู้ร่วมโครงการทั้งหมด 36 คนมีอายุเฉลี่ย 63.9 + 3.66 ปี ค่าเฉลี่ย T-Score ของมวลรวมกระดูกที่บริเวณกระดูกสันหลัง และสะโพก -2.96 + 0.87 และ -2.96 + 0.77 กรัม/ซม.^{2} การลดลงของระดับ ซีเทอร์มินอลในกลุ่มที่รับประทานแคลเซี่ยมก่อนนอนต่ำกว่ากลุ่มที่รับประทานช่วงหลังอาหาร 2 มื้อ อย่างมีนัยสำคัญทางสถิติ (0.228 + 0.002 นก./มล. และ 0.313 + 0.003 นก./มล., $p < 0.001$) ค่าเฉลี่ยของระดับพาราธัยรอยด์ฮอร์โมนในกลุ่มที่รับประทานแคลเซี่ยมก่อนนอนต่ำกว่ากลุ่มที่รับประทานในช่วงหลังอาหาร 2 มื้อ อย่างมีนัยสำคัญทางสถิติ (25.17 + 2.31 พก./มล. และ 31.930 + 2.677 พก./มล., $p < 0.001$)*

สรุป: *การรับประทานแคลเซี่ยมเสริมช่วงก่อนนอนพบว่ามีประสิทธิภาพในการลดระดับค่าดัชนีชี้วัดการสลายตัวของมวลกระดูก และระดับพาราธัยรอยด์ฮอร์โมนได้ดีกว่าการรับประทานแคลเซี่ยมเสริมช่วงหลังอาหาร 2 มื้อในระยะเวลาสั้น ๆ แต่ประสิทธิภาพของยาในระยะยาวยังต้องการการศึกษาต่อไปข้างหน้า*