Influence of Normal Ageing on Mechanism of Bone Loss in Women and Men in Bangkok

LA-OR CHAILURKIT, Ph.D.*,
NOPPAWAN PIASEU, B.Sc., M.Sc.*,
RAJATA RAJATANAVIN, M.D.*

Abstract

Age and sex related changes in bone metabolism are of interest in the pathogenesis of osteoporosis. However, most data in the literature were studied in Western countries. In a tropical country, such as Thailand, little is known of vitamin D status and bone remodeling. Thus, the aim of this study was to determine the changes of vitamin D levels and biochemical markers of bone turnover in healthy women and men of various age groups between 20-80 years who were living in Bangkok. From the results, vitamin D levels of various age groups did not alter significantly between men and women except in the sixth decade of women. However, men had higher levels of vitamin D than women. In women, all biochemical markers of bone turnover increased with age, with a sharp increase at the onset of menopause. In contrast, biochemical markers of bone turnover in men gradually declined with advancing age.

Conclusion : There was no evidence of vitamin D deficiency in the Bangkok population. Women and men showed different age-related changes in bone metabolism.

Key word : Vitamin D, Bone Markers, Bone Loss

CHAILURKIT L, PIASEU N, RAJATANAVIN R
J Med Assoc Thai 2002; 85: 915-921

Bone loss is a universal phenomenon with ageing and it occurs in all individuals after middle age. The mechanisms of bone loss are multifactorial. The major factors are likely to be mediated by a combination of hormonal and nutritional factors that impair regulation of calcium homeostasis. Vitamin D is a unique hormone which is essential for the maintenance of a healthy skeleton throughout our lives. Geographic location, seasonal variations, skin pigments, social conditions, aging and nutritional habits

* Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

are known to influence serum vitamin D level[1,2]. A low vitamin D level in serum identifies subjects at high risk of developing bone disease. Numerous studies have reported that vitamin D deficiency is a common problem in elderly people. However, much of these data were from Western countries[3-7]. In tropical countries with plenty of sunlight such as Thailand, there is a paucity of information on the influence of normal aging on vitamin D status and the changes in bone remodeling which can be examined by measuring the levels of biochemical markers of bone turnover. An important clinical application of these biochemical markers lies in their ability to predict the rate of bone loss and subsequent risk of fractures[8-10]. A high level of a marker indicates a high bone turnover and consequently, a high rate of bone loss[11,12] which may lead to a higher fracture incident rate. Recently, newer biochemical markers of bone turnover have been developed and shown to have a clear advantage over older markers which have low specificity and sensitivity[13-15]. These new markers allow clinicians to identify individual patients with high bone turnover and to monitor interventions to slow bone loss.

As the mean age of the population increases, more attention is being paid to diseases associated with ageing, including diseases of the skeleton such as osteoporosis. Assessment of vitamin D status and the levels of biochemical markers of bone turnover of the population may provide clinically relevant information about skeletal remodeling for predicting future bone loss and may be important for primary care in preventing osteoporosis. Therefore, the aim of this study was to determine the changes of vitamin D levels and biochemical markers of bone turnover with ageing among normal healthy subjects living in Bangkok and its vicinity.

MATERIAL AND METHOD

Subjects

The participants were recruited from 396 people who were living in Bangkok and its vicinity. There were 155 men and 241 women, aged 20-80 years. All were in good health. All had neither signs or symptoms of metabolic or hormonal diseases (particularly those known to affect bone or calcium metabolism) nor any history of fracture. The participants were excluded from the study if they were taking corticosteroid or calcium supplement, or were receiving hormone replacement therapy. The study was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, and informed consent was obtained from all study participants. The participants were stratified into 6 groups according to their age.

Laboratory assays

Blood samples were collected between 8.00 a.m. and 9.00 a.m. after an overnight fast. Sera were kept frozen at -80°C until assayed. Serum 25 hydroxyvitamin D (25 OHD) was measured by radioimmunoassay (DiaSorin Inc., Stillwater, USA). Serum total alkaline phosphatase (ALP) was measured by automated enzymatic method (Selectra, Vital Scientific, Netherlands). Serum N-terminal mid fragment osteocalcin (OC (1-43)) and serum carboxy terminal telopeptide fragment of type I collagen (CTX-I) were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Germany). The within-assay coefficient of variations (CVs) of serum 25 OHD, OC (1-43) and CTX-I were, respectively, 15.8 per cent, 1.0 per cent, 3.4 per cent and of between-assay CVs were 14.4 per cent, 5.1 per cent, 4.1 per cent, respectively, at mean concentrations of 83.4 ng/ml, 20.5 ng/ml, and 0.41 ng/ml.

Statistical analyses

All data are presented as mean ± SE unless stated otherwise. Comparisons between groups were analyzed by Student's unpaired *t*-test or Mann-Whitney U test. The statistical significance among age groups in the same sex was determined with one-way analysis of variance followed by Scheffe F test or with Kruskal-Wallis test. All analyses were performed using SPSS/PC release 10.01.

RESULTS

The levels of serum 25 OHD, total ALP, OC (1-43) and CTX-I of each age group in both sexes are presented in Table 1 and Table 2.

In women, menopausal age was 49.6 ± 4.3 (mean ± SD) years. The mean levels of 25 OHD, total ALP, OC (1-43) and CTX-I in premenopausal age groups (the third through fifth decade) did not change significantly (Fig. 1). However, only the mean serum CTX-I in the third decade was found significantly higher than that of the fifth decade. In postmenopausal age, the mean serum 25 OHD and total ALP in the sixth decade was significantly higher than that of the fifth decade; both gradually decreased

Table 1. Serum vitamin D and biochemical markers of bone turnover levels in women.

Age	N	Women			
		25 OHD	Total ALP	OC (1-43)	CTX-I
20-29	28	33.68 ± 2.68 (n=22)	18.52 ± 0.83	20.19 ± 1.10	0.35 ± 0.02
30-39	30	29.10 ± 2.39 (n=23)	16.60 ± 0.93	19.91 ± 1.27	0.28 ± 0.02
40-49	57	32.61 ± 2.90 (n=17)	18.24 ± 0.90	17.52 ± 0.97	0.28 ± 0.01
50-59	50	51.65 ± 4.66 (n=20)	22.44 ± 1.01	28.76 ± 1.46	0.54 ± 0.03
60-69	50	38.77 ± 5.0 (n=20)	21.39 ± 1.02	30.37 ± 1.91	0.54 ± 0.03
70-80	26	37.79 ± 4.14 (n=19)	19.28 ± 1.12	29.37 ± 2.54	0.53 ± 0.04

Values are mean ± SE, N = number
25 OHD = 25 hydroxyvitamin D, ALP = alkaline phosphatase, OC (1-43) = N-terminal mid fragment osteocalcin, CTX-I = carboxy terminal telopeptide fragment of type I collagen.

Table 2. Serum vitamin D and biochemical markers of bone turnover levels in men.

Age	N	Men			
		25 OHD	Total ALP	OC (1-43)	CTX-I
20-29	24	52.04 ± 6.08 (n = 14)	19.12 ± 1.21	27.85 ± 2.14	0.56 ± 0.05
30-39	27	54.07 ± 5.30 (n=18)	18.71 ± 1.14	22.01 ± 0.86	0.43 ± 0.02
40-49	25	59.79 ± 7.10 (n=16)	22.28 ± 1.51	22.23 ± 1.59	0.44 ± 0.03
50-59	25	53.14 ± 4.92 (n=20)	22.12 ± 1.17	19.36 ± 1.77	0.39 ± 0.03
60-69	28	36.09 ± 3.26 (n=20)	20.36 ± 1.28	19.10 ± 1.26	0.37 ± 0.03
70-80	26	52.05 ± 4.80 (n=20)	18.83 ± 1.18	20.00 ± 1.36	0.34 ± 0.02

Values are mean ± SE, N = number
25 OHD = 25 hydroxyvitamin D, ALP = alkaline phosphatase, OC (1-43) = N-terminal mid fragment osteocalcin, CTX-I = carboxy terminal telopeptide fragment of type I collagen.

through the eighth decade. In contrast, the mean serum OC (1-43) and CTX-I significantly increased in the fifth decade and remained stable up to the eighth decade.

In men, there were no significant changes of serum 25 OHD levels between age groups (Fig. 1). Serum total ALP slightly increased in the fifth decade. Thereafter, it gradually decreased up to the eight decade. However, these changes were small and without statistical significance compared to that of the third decade. Serum OC (1-43) and CTX-I levels decreased gradually from the third through eighth decade. In the sixth decade, serum OC (1-43) and CTX-I were observed to decrease significantly from the third decade and continued to decrease through to the eighth decade.

Compared with women in the same age groups, men had higher levels of serum 25 OHD than women. However, the higher levels of 25 OHD in men at the sixth and seventh decades did not significantly differ from those of women. A significant gender difference was not observed for serum total ALP except in the fifth decade. In the younger age groups (20-49 years), mean serum levels of OC (1-43) and CTX-I were significantly higher in men than in women. However, mean serum OC (1-43)

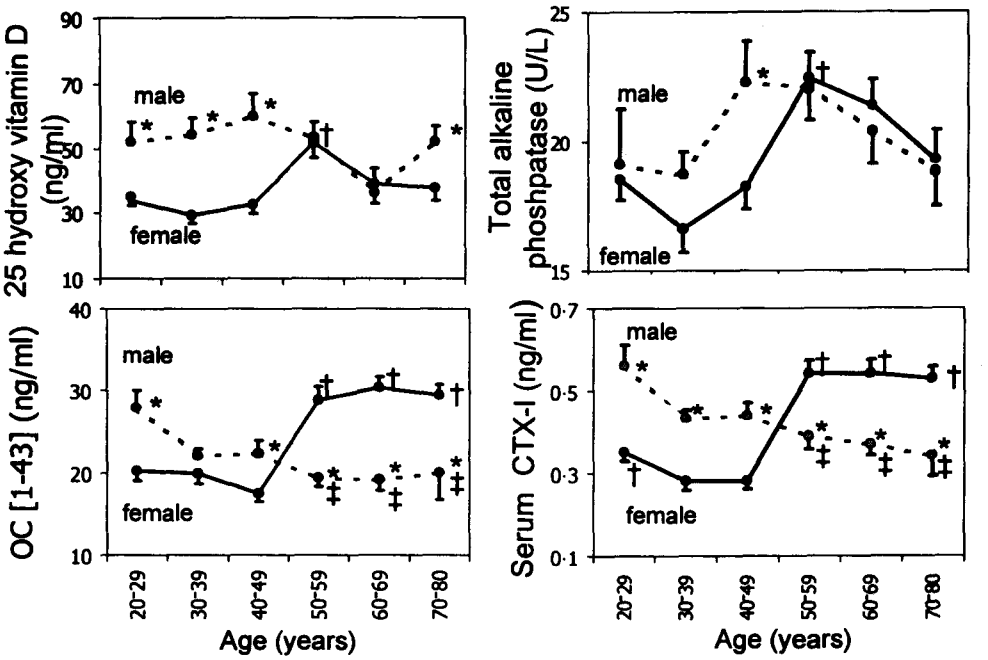

Fig. 1. Changes in serum 25 OHD, total ALP, OC (1-43) and CTX-I with age in women and men. Value are mean ± SE. * p<0.05 *vs* women at the same age group, † p<0.05 *vs* the fifth decade in women, ‡ p<0.05 *vs* the third decade in men.

levels in the fourth decade in men and women were not different. After the fifth decade, both serum OC (1-43) and CTX-I in men were significantly lower than those in women.

DISCUSSION

Serum 25-OHD concentrations of people living in Bangkok and its vicinity were high, especially in elderly subjects. This finding was similar to a previous report by the authors on subjects in Khon Kaen province[16]. However, the levels of 25 OHD of Khon Kaen subjects did not change with ageing in either sex. In contrast, most previous studies have shown that plasma levels of 25(OH) D decreased with ageing in both men and women[17-19]. The discrepancy between the authors' data and other results may be explained by greater availability of sunlight in the lower latitude area of this country. Nevertheless, the excellent vitamin D status in Bangkok elderly subjects might be due to the higher educational and socioeconomic status and greater nutritional consciousness than others. In addition, men had higher level of serum 25 OHD than women. This might be due to more outdoor activities in men. Therefore, vitamin D deficiency in Thailand is probably not a major risk factor for osteoporosis in active elderly.

With regard to biochemical markers of bone turnover, both bone formation and resorption markers in women were shown to increase markedly at the onset of menopause. These results were in agreement with those of others[20,21]. It is relevant that the values of biochemical markers of bone turnover were associated with the degree of the change in bone mass, therefore, these data suggested that accelerated bone loss occurred in the early postmenopausal period. An important determinant of rapid bone loss is estrogen deficiency. In addition, recent studies using bone metabolic markers have revealed that high bone turnover at menopause continued for a longer period than previously expected[22-24]. The present study also demonstrated that the levels of OC (1-43) and CTX-I remained high during the post-menopause period for up to 20 years. This indicated that increased bone turnover continues to be present in the post-menopausal period in healthy women. Sustained bone loss in late postmenopausal women could lead to

osteoporosis. Therefore, It would be necessary to implement preventive therapy on osteoporosis soon after menopause. Bone loss in men is likely due to decreased functional capacity of bone cells associated with the aging process, which results in impaired bone formation relative to bone resorption[25,26]. This concept was compatible with a decline in biochemical markers of bone turnover with age in the present study and was also supported by histomorphometric studies[27,28]. However, the changes of total ALP activity with age were not compatible with the levels of OC (1-43) and CTX-I in both women and men. The failure of total ALP activity to follow the pattern of other biochemical markers of bone turnover probably reflects the poor specificity of this parameter. Circulating levels of ALP are derived from many sources other than bone[29,30]. Therefore, further studies using bone specific alkaline phosphatase as a bone formation marker would be interesting. Moreover, the levels of biochemical markers of bone turnover were higher in men than in women between the ages of 20 and 50. In contrast, after the ages of 50, all three biochemical markers of bone turnover in men were lower than in women. Therefore, the loss of bone and bone fragility occurred less in men than in women.

SUMMARY

There was no evidence of vitamin D deficiency in people living in Bangkok and its vicinity. Women and men showed a different pattern of age-related changes in biochemical markers of bone turnover. The cessation of gonadal function is the importance factor of an increase in bone turnover in women at the time of menopause.

ACKNOWLEDGEMENT

This work was supported by the Anandamahidol Foundation.

(Received for publication on April 11, 2002)

REFERENCES

1. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr 1988; 8: 375-99.
2. Katz BS, Jackson GJ, Hollis BW, Bell NH. Diagnostic criteria of vitamin D deficiency. The Endocrinologist 1993; 3: 248-53.
3. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. Am J Clin Nutr 1990; 51: 1075-81.
4. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK. Vitamin D status in the elderly: Seasonal substrate deficiency causes 1, 25-dihydroxycholecalciferol deficiency. Am J Clin Nutr 1987; 45: 755-63.
5. Rosen CJ, Morrison A, Zhou H, et al. Elderly women in northern New England exhibit seasonal changes in bone mineral density and calciotropic hormones. Bone Miner 1994; 25: 83-92.
6. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. N Engl J Med 1989; 321: 1777-83.
7. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Seasonal variation in the incidence of hip fracture among white persons aged 65 years and older in the United States, 1984-1987. Am J Epidemiol 1991; 133: 996-1004.
8. Delmas PD. How should the risk of fracture in postmenopausal women be assessed? Osteoporos Int 1999; 9 (Suppl 2): S33-9.
9. Dresner-Pollak R, Parker RA, Poku M, Thompson J, Seibel MJ, Greenspan SL. Biochemical markers of bone turnover reflect femoral bone loss in elderly women. Calcif Tissue Int 1996; 59: 328-33.
10. Ross PD, Knowlton W. Rapid bone loss is associated with increased levels of biochemical markers. J Bone Miner Res 1998; 13: 297-302.
11. Christiansen C, Riis BJ, Rodbro P. Prediction of rapid bone loss in postmenopausal women. Lancet 1987; 1: 1105-8.
12. Johansen JS, Riis BJ, Delmas PD, Christiansen C. Plasma BGP: An indicator of spontaneous bone loss and of the effect of oestrogen treatment in postmenopausal women. Eur J Clin Invest 1988; 18: 191-5.
13. Chailurkit L, Ongphiphadhanakul B, Piaseu N,

Saetung S, Rajatanavin R. Biochemical markers of bone turnover and response of bone mineral density to intervention in early postmenopausal women: An experience in a clinical laboratory. Clin Chem 2001; 47: 1083-8.

14. Fink E, Cormier C, Steinmetz P, Kindermans C, Le Bouc Y, Souberbielle JC. Differences in the capacity of several biochemical bone markers to assess high bone turnover in early menopause and response to alendronate therapy. Osteoporos Int 2000; 11: 295-303.
15. Dessauer A. Analytical requirements for biochemical bone marker assays. Scand J Clin Lab Invest 1997; 227 (Suppl): 84-9.
16. Chailurkit L, Pongchaiyakul C, Charoenkiatkul S, Kosulwat V, Rojroongwasinkul N, Rajatanavin R. Different mechanism of bone loss in ageing women and men in Khon Kaen Province. J Med Assoc Thai 2001; 84: 1175-82.
17. Aksnes L, Rodland O, Odegaard OR, Bakke KJ, Aarskog D. Serum levels of vitamin D metabolites in the elderly. Acta Endocrinol (Copenh) 1989; 121: 27-33.
18. Lund B, Sorensen OH. Measurement of 25-hydroxyvitamin D in serum and its relation to sunshine, age and vitamin D intake in the Danish population. Scand J Clin Lab Invest 1979; 39: 23-30.
19. Tsai KS, Wahner HW, Offord KP, Melton LJ 3rd, Kumar R, Riggs BL. Effect of aging on vitamin D stores and bone density in women. Calcif Tissue Int 1987; 40: 241-3.
20. Uebelhart D, Schlemmer A, Johansen JS, Gineyts E, Christiansen C, Delmas PD. Effect of menopause and hormone replacement therapy on the urinary excretion of pyridinium cross-links. J Clin Endocrinol Metab 1991; 72: 367-73.
21. Forgelman I, Poser JW, Smith ML, Hart DM, Bevan JA. Alterations in skeletal metabolism following oophorectomy. In: Christiansen C, Arnaud CD, Nordin BEC, Parfitt AM, Peck WA, Riggs BL, Eds. Osteoporosis: Proceedings Copenhagen international symposium on osteoporosis. Glostrup, Denmark: Aalborg Stiftsbogtrykkeri, 1984: 519-21.
22. Takahashi M, Kushida K, Hoshino H, Ohishi T, Inoue T. Biochemical markers of bone turnover do not decline after menopause in healthy women. Br J Obstet Gynaecol 1999; 106: 427-31.
23. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res 1996; 11: 337-49.
24. Sokoll LJ, Sadowski JA. Comparison of biochemical indexes for assessing vitamin K nutritional status in a healthy adult population. Am J Clin Nutr 1996; 63: 566-73.
25. Parfitt AM. The coupling of bone formation to bone resorption: A critical analysis of the concept and of its relevance to the pathogenesis of osteoporosis. Metab Bone Dis Relat Res 1982; 4: 1-6.
26. Marie PJ, de Vernejoul MC, Connes D, Hott M. Decreased DNA synthesis by cultured osteoblastic cells in eugonadal osteoporotic men with defective bone formation. J Clin Invest 1991; 88: 1167-72.
27. Kurland ES, Rosen CJ, Cosman F, et al. Insulin-like growth factor-I in men with idiopathic osteoporosis. J Clin Endocrinol Metab 1997; 82: 2799-805.
28. Reed BY, Zerwekh JE, Sakhaee K, Breslau NA, Gottschalk F, Pak CY. Serum IGF 1 is low and correlated with osteoblastic surface in idiopathic osteoporosis. J Bone Miner Res 1995; 10: 1218-24.
29. Delmas PD. Biochemical markers of bone turnover. J Bone Miner Res 1993; 8 (Suppl 2): S549-55.
30. Moss DW. Alkaline phosphatase isoenzymes. Clin Chem 1982; 28: 2007-16.

อิทธิพลของอายุที่มีผลต่อการสูญเสียมวลกระดูกในเพศหญิงและชายที่อาศัยอยู่ในเขตกรุงเทพมหานครและปริมณฑล

ละออ ชัยลือกิจ, ปร.ด.,*
นพวรรณ เปียซื่อ, วท.บ., วท.ม., รัชตะ รัชตะนาวิน, พ.บ.**

ในประเทศทางแถบตะวันตกได้มีรายงานว่าระดับวิตามินดีและดัชนีทางเคมีของการสร้างและสลายมวลกระดูกมีการเปลี่ยนแปลงตามอายุและเพศ แต่ในทางประเทศตะวันออกโดยเฉพาะประเทศที่ตั้งอยู่ในภูมิประเทศทางเขตร้อนมีข้อมูลเหล่านี้น้อยมากโดยเฉพาะในประเทศไทย ดังนั้นคณะผู้วิจัยจึงทำการวัดระดับวิตามินดีและดัชนีทางชีวเคมีของการสร้างและสลายมวลกระดูกทั้งเพศหญิงและชายในช่วงอายุต่าง ๆ ระหว่าง 20 ถึง 80 ปี ที่อาศัยอยู่ในเขตกรุงเทพ ฯ และปริมณฑล

จากการศึกษาพบว่าระดับวิตามินดีของประชากรที่อาศัยอยู่ในเขตกรุงเทพ ฯ และปริมณฑลไม่มีการเปลี่ยนแปลงตามอายุทั้งในเพศหญิงและชาย (ยกเว้นเพศหญิงในกลุ่มอายุ 50–59 ปี) อย่างมีนัยสำคัญทางสถิติ นอกจากนั้นยังพบว่าในช่วงอายุที่เท่ากันเพศชายมีระดับวิตามินดีสูงกว่าเพศหญิง ส่วนการศึกษาดัชนีทางชีวเคมีของการสร้างและสลายมวลกระดูก พบว่าดัชนีดังกล่าวในเพศหญิงมีระดับสูงขึ้นตามอายุ และดัชนีเหล่านี้มีระดับสูงขึ้นมากอย่างรวดเร็วเมื่อเริ่มเข้าสู่วัยหมดประจำเดือน ในทางตรงกันข้าม ดัชนีดังกล่าวในเพศชายกลับมีระดับลดลงช้า ๆ อย่างต่อเนื่องตามอายุ

สรุปได้ว่าประชากรที่อาศัยอยู่ในเขตกรุงเทพ ฯ และปริมณฑลไม่ขาดวิตามินดี เพศหญิงและเพศชายมีกลไกการเปลี่ยนแปลงทางเมตาบอลิสม์ของกระดูกแตกต่างกัน

คำสำคัญ : วิตามินดี, ดัชนีของกระดูก, การสูญเสียมวลกระดูก

ละออ ชัยลือกิจ, นพวรรณ เปียซื่อ, รัชตะ รัชตะนาวิน
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 915–921

* ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400