serum 25(OH)D concentration ($P < 0.05$; Table 3). The mean intake of vitamin D was significantly correlated with the intake of fish (Spearman; $r = 0.74$, $P < 0.001$).

Of the items examined for physical activity, the mean daily energy expenditure on exercise and the number of steps taken per day as calculated based on the accelerometer were significantly associated with the serum 25(OH)D concentration. Analysis of the daily time allocation showed that the mean time spent in sedentary activity was negatively correlated with the serum 25(OH)D concentration.

The estimated duration of exposure to sunlight as calculated from the time spent on outdoor activities showed no significant association with the serum 25(OH)D concentration.

The vitamin D intake, the steps taken per day and the time spent in sedentary activity were chosen for stepwise multiple regression analysis, with the 25(OH)D concentration as the outcome variable ($P < 0.05$). As a result, each of these factors was found to significantly impact the 25(OH)D concentration (Table 4), while the r values were small.

Table 3 Correlation coefficients (r) for serum 25(OH)D levels versus lifestyle factors

Variable	r	P
Selected nutrient and food intakes assessed by the DHQ		
Calcium (mg/1000 kcal)	0.11	0.077
Vitamin D (μg/1000 kcal)	0.20	0.001
Fish (mg/kcal)	0.18	0.002
Egg (g/1000 kcal)	0.07	0.249
Physical activity		
As assessed by the JALSPAQ		
Total energy expenditure (METs-h/day)	0.08	0.164
Sedentary activity (h)	−0.14	0.018
As assessed by the accelerometer[a]		
Total energy expenditure (kcal/day)	0.07	0.265
Energy expenditure for exercise (kcal/day)	0.15	0.016
Steps (steps/day)	0.16	0.009
Exposure to sunlight[a] (h/day)	0.04	0.487

Spearman's rank correlation coefficient

DHQ Diet History Questionnaire, *JALSPAQ* the Physical Activity Questionnaire by the Japan Arteriosclerosis Longitudinal Study

[a] Duration of exposure to sunlight was calculated from the questionnaire responses: amount of time spent on traveling to and from places (i.e., to work, for shopping), outdoor leisure time activities considered to involve exposure to sunlight

Table 4 Lifestyle factors showing significant correlation to serum 25(OH)D

Variable	Parameter estimate	Standard estimate	P	R^2	Model R^2
Vitamin D (μg/1000 kcal)	0.258	3.724	0.001	0.037	0.084
Steps (number/day)	0.000	2.147	0.010	0.024	
Sedentary activity (h)	−0.287	−2.039	0.038	0.015	

Stepwise multiple regression analysis

Discussion

Vitamin D and PTH have an important role in controlling the plasma calcium concentration. Any fall in the ionized calcium concentration is detected by the calcium receptor of the parathyroid gland, followed by the secretion of PTH by the parathyroid gland. PTH then activates vitamin D production, which in turn promotes calcium absorption from the intestines, increases bone resorption by the osteoclasts and compensates for the plasma calcium concentration which is accompanied by the reduction of calcium accumulated in the bone [23].

Insufficient intake of vitamin D is known to cause untoward conditions, such as secondary hyperparathyroidism and decreased BMD [3], and vitamin D deficiency is known to be a significant risk factor for osteoporosis and secondary hyperparathyroidism. Vitamin D, as it results from both cutaneous production and from dietary intake, reflects the conditions of daily living. Around 80–90% of (the precursor of) vitamin D is absorbed through the intestines or produced at the skin through exposure to sunlight, becoming a biologically active hormone after hydration [24]. It is thus recommended that hands, face and arms, or arms and legs, be exposed to sunlight for a period equal to 25% of the time required to cause a light pinkness to the skin [25]. Vitamin D intake varies from country to country [14]. The standard value recommended for intake of dietary vitamin D is 5 μg for 15–18-year-olds in Japan.

Serum 25(OH)D concentration is the best clinical indicator of the vitamin D concentration in blood. The serum 25(OH)D concentration is lower in the elderly [26, 27], lower in women than in men [27] and lower in winter than in the other seasons [1, 25]. Low concentrations of 25(OH)D, defined as below 25 nmol/L, lead to an increase in the serum PTH concentration and to increased bone resorption [2]. Insufficiency of 25(OH)D in youth is associated with low BMD of the forearm [28] and hampers acquisition of maximum peak bone mass at the lumbar spine [29]. In addition, it is reported in a study evaluating BMD of the calcaneus that low levels of 25(OH)D may adversely affect bone strength [12].

In this study, we measured serum 25(OH)D levels using Nichols Advantage CLPBA. It detects serum 25(OH)D2 with much less sensitivity than serum 25(OH)D3. In Japan, vitamin D2 preparations are not prescribed for patients and vitamin D2 supplements are less used. Furthermore, we had

reported that the ratio of 25(OH)D2 to total serum 25(OH)D in Japanese was extremely small [30]. Therefore, there is no doubt that the 25(OH)D2 levels as measured on the Nichols Advantage did not affect our study results.

We investigated the association between serum 25(OH)D, intact PTH levels and BMD. The serum 25(OH)D concentration is negatively correlated with intact PTH. The low intact PTH and high 25(OH)D group showed higher serum calcium concentrations and BMD than the other group. Background data including age, BMI, serum parameters and birth information were not significantly different between the two groups. High 25(OH)D levels were assumed to control the intact PTH level, and to contribute toward an increase in calcium absorption and, consequently, in BMD.

Analysis of the lifestyle factors showed that exposure to sunlight had no impact on serum 25(OH)D. Previous study reports indicated positive correlation between sunlight exposure and serum 25(OH)D [24, 25]. But this study indicated no correlation between them. We estimated the reasons for this discrepancy as follows. First, the amount of vitamin D synthesis by sunlight reaches the upper limit of normal in Tokyo, at 35° north latitude [26]. Furthermore, Hollis et al. reported that an adequate UVB exposure level (18–20 mJ/cm^2) in sunlight to induce pre-vitamin D on the epithelium is not generally reached during winter in the northern United States above latitude 40° [10]. Second, the measurement of sunlight exposure time may have some methodological problems. However, our results showing no association between the estimated time of exposure to sunlight and the serum 25(OH)D level did not contradict the positive correlation between sunlight exposure and serum 25(OH)D. Landin-Wilhelmsen et al. have reported that physical activities are often associated with being outdoors, and active individuals should therefore have a better chance of having sun exposure [8]. On the contrary, our study showed that there was no significant correlation between sunlight exposure and serum 25(OH)D levels. We might speculate that our participants may have applied some ultraviolet protection cosmetics when they exercised, though we did not check on it. That's likely the reason why only physical activities correlated with 25(OH)D.

Dietary intake of vitamin D (including supplements) and fish had an impact on serum 25(OH)D (Table 3). The participants consumed 56.9 ± 45.4 g of fish per day, which was found to be significantly correlated with vitamin D. The steps taken per day or energy expenditure on exercise had a positive impact, while the time spent in sedentary activity (watching TV, playing computer games) had a negative impact on serum 25(OH)D, suggesting that physical activity acted in an additive manner with vitamin D intake in Japanese young women. Although there have been reports showing correlation between physical activity and serum 25(OH)D [8, 9], the present study was too small to draw any conclusion in this regard. Calcium is the most abundant of minerals available in the human body, of which 99% is found in bone with the rest in blood and muscle. Vitamin D participates in the contraction of muscle and is known to maintain myodynamia by transporting calcium from bone to muscle when it is calcium-deficient. Moreover, Kwon et al. reported that concomitant low serum albumin and vitamin D levels are associated with decreased muscle strength and balancing capability in elderly people [21].

The present study had several limitations. First, this cohort study was confined in geographical coverage to Tokyo only. Therefore, the distribution of the research parameter sunlight exposure could have been narrow. Second, participants were only students or nurses by occupation, possibly suggesting a similar lifestyle pattern among the participants. And third, since sunlight exposure was estimated from the JALSPAQ, the use of ultraviolet protection cosmetics was not able to be ruled out.

However, this is the first report investigating the association between the impact of lifestyle factors and serum 25(OH)D levels in Japanese young women which appears to partially explain the correlation between the steps taken per day and the serum 25(OH)D level. Further research is needed to verify the reported correlation between physical activity and serum 25(OH)D.

In conclusion, the serum 25(OH)D concentration was positively affected by dietary vitamin D or fish intake and the mean steps taken per day or energy expenditure on exercise, and was negatively affected by the time spent in sedentary activity. These findings may suggest that lifestyle modification at an early age may contribute to preventing osteoporosis or frailty in later years.

Acknowledgments This work was partly supported by a Grant-in-aid from Japan Osteoporosis Foundation. The authors thank Dr. Hiroya Okano, Dr. Ken Ishitani and Dr. Yuko Miyabara for their help in maintaining the Peak Bone Mass Study as well as for their data collection and stimulating discussions.

References

1. Holick MF (1995) Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 61:638S–645S
2. Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of the Food Nutrition Policy: subgroup on the Nutritional Aspects of Bone Health. 49 Nutrition and bone health: with particular reference to calcium and vitamin D. Report of the Subgroup on Bone Health (1998) Rep Health Soc Subj. The Stationary Office, London, iii–xvii, p 1–24
3. Sahota O, Mundey MK, San P, Godber IM, Lawson N, Hosking DJ (2004) The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. Bone 35:312–319

4. Lips P (2001) Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 22:477–501
5. Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B (1998) Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 339:733–738
6. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB (2004) Effect of Vitamin D on falls: a meta-analysis. JAMA 291:1999–2006
7. Souberbielle JC, Cormier C, Kindermans C, Gao P, Cantor T, Forette F, Baulieu EE (2001) Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. J Clin Endocrinol Metab 86:3086–3090
8. Landin-Wilhelmsen K, Wilhelmsen L, Wilske J, Lappas G, Rosén T, Lindstedt G, Lundberg PA, Bengtsson BA (1995) Sunlight increases serum 25(OH) vitamin D concentration whereas 1, 25(OH)2D3 is unaffected. Results from a general population study in Goteborg, Sweden (The WHO MONICA Project). Eur J Clin Nutr 49:400–407
9. van Dam RM, Snijder MB, Dekker JM, Stehouwer CD, Bouter LM (2007) Potentially modifiable determinants of vitamin D status in an older population in the Netherlands: the Hoorn Study. Am J Clin Nutr 85:755–761
10. Hollis BW (2005) Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 135:317–322
11. Nakamura K, Nashimoto M, Hori Y, Yamamoto M (2000) Serum 25-hydroxyvitamin D concentrations and related dietary factors in peri- and postmenopausal Japanese women. Am J Clin Nutr 71:1161–1165
12. Nakamura K, Nashimoto M, Matsuyama S, Yamamoto M (2001) Low serum concentrations of 25-hydroxyvitamin D in young adult Japanese women: a cross sectional study. Nutrition 17:921–925
13. Nakamura K, Nashimoto M, Tsuchiya Y, Obata A, Miyanishi K, Yamamoto M (2001) Vitamin D insufficiency in Japanese female college students: a preliminary report. Int J Vitam Nutr Res 71:302–305
14. Calvo MS, Whiting SJ, Barton CN (2005) Vitamin D intake: a global perspective of current status. J Nutr 135:310–316
15. Miyabara Y, Onoe Y, Harada A, Kuroda T, Sasaki S, Ohta H (2007) Effect of physical activity and nutrition on bone mineral density in young Japanese women. J Bone Miner Metab 25:414–418
16. Roth HJ, Zahn I, Alkier R, Schmidt H (2001) Validation of the first automated chemiluminescence protein-binding assay for the detection of 25-hydroxycalciferol. Clin Lab 47:365–367
17. Sasaki S, Yanagibori R, Amano K (1998) Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 8:203–215
18. Science and Technology Agency (2000) Standard tables of food composition in Japan, 5th edn. Printing Bureau, Ministry of Finance, Tokyo, Japan (in Japanese)
19. Sasaki S, Ushio F, Amano K, Morihara M, Todoriki O, Uehara Y, Toyooka E (2000) Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. J Nutr Sci Vitaminol (Tokyo) 46:285–296
20. Ainsworth B, Haskell W, Leon A, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr (1993) Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 25:71–80
21. Ainsworth B, Haskell W, Whitt M, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. (2000) Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32(suppl): S498–S516
22. Kumahara H, Schutz Y, Ayabe M, Yoshioka M, Yoshitake Y, Shindo M, Ishii K, Tanaka H (2004) The use of uniaxial accelerometry for the assessment of physical-activity-related energy expenditure: a validation study against whole-body indirect calorimetry. Br J Nutr 91:235–243
23. Willett AM (2005) Vitamin D status and its relationship with parathyroid hormone and bone mineral status in older adolescents. Proc Nutr Soc 64:193–203
24. Holick MF (2003) Evolution and function of vitamin D. Recent Results Cancer Res 164:3–28
25. Holick MF (2004) Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 79:362–371
26. Omdahl JL, Garry PJ, Hunsaker LA, Hunt WC, Goodwin JS (1982) Nutritional status in a healthy elderly population: vitamin D. Am J Clin Nutr 36:1225–1233
27. Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD (1982) Vitamin D and bone health in the elderly. Am J Clin Nutr 36:1014–1031
28. Outila TA, Karkkainen MU, Lamberg-Allardt CJ (2001) Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. Am J Clin Nutr 74:206–210
29. Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS (2002) Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. Am J Clin Nutr 76:1446–1453
30. Tsugawa N, Suhara Y, Kamao M, Okano T (2005) Determination of 25-hydroxyvitamin D in human plasma using high-performance liquid chromatography–tandem mass spectrometry. Anal Chem, May 1;77:3001–3007

J Bone Miner Metab (2009) 27:698–704
DOI 10.1007/s00774-009-0094-2

ORIGINAL ARTICLE

Age-related distribution of bone and skeletal parameters in 1,322 Japanese young women

Seiya Orito · Tatsuhiko Kuroda · Yoshiko Onoe · Yasuto Sato · Hiroaki Ohta

Received: 9 October 2008 / Accepted: 25 March 2009 / Published online: 12 May 2009

Abstract We explored factors that could serve as indices for therapeutic intervention aimed at prevention of osteoporosis. In this cross-sectional study, we investigated the timing of peak bone mass (PBM) in 1,322 Japanese women aged 12–30 years old. We measured height, body weight, bone mineral density (BMD), bone mineral content (BMC), and bone area at the lumbar spine and total hip, as well as the blood markers calcium, phosphorus, and the bone metabolic markers bone alkaline phosphatase (BAP) and type I collagen cross-linked N-telopeptide (NTX). All measurements were standardized with the mean at age 18 defined as 100% to identify age-related differences. In the total hip, BMD peaked at age 18, while, in the lumbar spine, BMD peaked at age 29, of which 99.8% was attained at age 18, suggesting that peak BMD was attained at age 18 at both the total hip and lumbar spine. No age difference was observed in serum calcium, while there was a 15.1% decrease between ages 12 and 18 in serum phosphorus. There were 273.8% and 208.5% decreases in serum BAP and NTX, respectively, between ages 12 and 18, while these levels remained constant thereafter, suggesting that bone and calcium metabolism are constant between ages 19 and 30. Factors that had stronger correlations with BMD, BMC, and bone area from 12 years to 18 years were height and body weight. PBM was reached at age 18. Control of body weight by using total hip BMD as an index for intervention should be reasonable.

Keywords Adolescence · Young adulthood · Bone mineral density · Peak bone mass · Bone metabolic markers

S. Orito · T. Kuroda · Y. Onoe · H. Ohta (✉)
Department of Obstetrics and Gynecology,
Tokyo Women's Medical University, 8-1 Kawada-cho,
Shinjuku-ku, Tokyo 162-8666, Japan
e-mail: ohtah@obgy.twmu.ac.jp

Y. Sato
Department of Hygiene and Public Health II,
Tokyo Women's Medical University, Tokyo, Japan

Introduction

Osteoporosis is widely recognized as an important public health problem because of the significant morbidity and even mortality associated with its complications, including fractures [1, 2]. While osteoporosis is primarily a disease affecting postmenopausal women, it is also a disease that reflects the bone status from early childhood to adolescence [3, 4]. Peak bone mass (PBM) is defined as a maximum amount of bone accrual in early life. Osteoporosis develops as a result of bone loss after the perimenopausal period [5], which is accounted for by two major causes: lower PBM and greater bone loss associated with aging [3, 4, 6]. Thus, in order to prevent onset of osteoporosis, it is considered important to keep bone mass from decreasing after the perimenopausal period and to obtain as high a PBM as possible in early life. Elucidating the timing of PBM is of critical importance as it allows an effective timing for intervention to be determined.

There are various reports in the literature on the timing of PBM. Some studies reported that peak bone mass is reached by late adolescence [7–11], whereas others reported bone mass gains, albeit small, during the third decade of life [12–16]. However, most studies reported that bone mass peaks at most sites by late adolescence [12, 15].

Thus, we aimed in this study to identify the optimal timing for intervention for osteoporosis and associated

indices for such intervention by determining the timing of PBM in 1,322 Japanese young healthy volunteers aged 12–30 years. In addition, we aimed to elucidate the age-related distribution of bone mineral density (BMD) at the lumbar spine and total hip as well as serum bone metabolic markers in these subjects.

Materials and methods

Subjects

In this cross-sectional cohort study, we recruited 1,322 Japanese women aged 12–30 years. The subjects were healthy volunteers composed of junior and senior high school students, nursing students at the School of Nursing and the Nursing Vocational School, both of which belong to Tokyo Women's Medical University, and nurses working at hospitals affiliated with the university. The subjects were excluded if they had systemic or metabolic disorders or were receiving medications that could affect bone metabolism. The study protocol was approved by the Ethics Committee of Tokyo Women's Medical University School of Medicine. Written consent was obtained from each subject. If a subject was under 20, written consent was obtained also from her guardian.

Measurements

Each subject completed a questionnaire on her background including age at the time of study entry, age at menarche, birth weight, gestational age at birth, and current menstrual status. We measured height and body weight. The bone parameters BMD, bone mineral content (BMC), and bone area were assessed at the lumbar spine (L2–L4) and the total hip or the femoral neck by using dual-X ray absorptiometry (DXA) (QDR-4500 absorptiometer; Hologic Inc., Bedford, MA). Fasting blood samples were taken simultaneously and routine blood chemistry tests were performed by SRL, Inc. to measure serum calcium, phosphorus, albumin, and the bone metabolic markers, bone alkaline phosphatase (BAP) and type I collagen cross-linked N-telopeptide (NTX).

Statistical analysis

Continuous parameters were expressed as mean ± SD to describe the subjects. Height, body weight, BMD, BMC, bone area, serum calcium, phosphorus, BAP, and NTX values were standardized by the mean at age 18 defined as 100% to evaluate age-related differences. We evaluated relevant parameters with the Spearman rank-order correlation to see if they might serve as potential indices for intervention in BMD, BMC, and bone area.

Results

Age-related distribution of the measured values

The characteristics of the 1,322 subjects are shown in Table 1. The number of subjects who had not yet experienced menarche were 42 at age 12 (35.6% of those their age), 24 at age 13 (24.5%), 11 at age 14 (9.9%), and 3 at age 15 (2.8%).

The age-related distribution of skeletal parameters (height and body weight) is shown in Fig. 1. Maximum mean height was 159.8 cm at age 18, with subjects' height remaining almost constant thereafter. Maximum mean weight was 55.3 kg at age 21, with subjects' weight continuing to increase even after their height stopped increasing.

Maximum mean BMD in the total hip was 0.934 g/cm^2 at age 18, while that in the lumbar spine was 1.027 g/cm^2 at age 29, of which 99.8%, 1.025 g/cm^2, was attained at age 18 (Fig. 2a). Maximum BMC in the total hip was 29.1 g at age 18, while that in the lumbar spine was 48.4 g at age 29, of which 95.2%, 44.2 g, was attained at age 18 (Fig. 2b). Maximum mean bone area in the total hip was 32.6 cm^2, of which 95.8%, 31.2 cm^2, was attained at age 18, while that in the lumbar spine was 45.4 cm^2 at age 23, of which 94.7%, 43.0 cm^2, was attained at age 18 (Fig. 2c).

Table 1 Characteristics of all subjects

Variables	*n*	Mean	SD
Age (years)	1,322	19.5	5.6
Height (cm)	1,322	157.5	5.5
Weight (kg)	1,322	50.2	7.6
BMI (kg/m^2)	1,322	20.2	2.6
Age at menarche (years)	1,229	12.0	1.2
Birth weight (g)	1,222	3,101	431
Gestational age at birth (weeks)	981	39.2	1.8
Lumbar spine			
BMD (g/cm^2)	1,322	0.961	0.119
BMC (g)	1,322	41.2	8.1
Bone area (cm^2)	1,322	42.6	4.5
Total hip			
BMD (g/cm^2)	1,322	0.879	0.106
BMC (g)	1,322	26.9	4.5
Bone area (cm^2)	1,322	30.5	3.3
Serum markers			
Calcium (mg/dL)	1,322	9.6	0.4
Phosphorus (mg/dL)	1,322	4.0	0.5
Albumin (g/dL)	1,322	4.8	0.2
BAP (U/L)	1,322	41.2	37.9
NTX (nmol BCE/L)	1,322	8.2	12.4

BMD bone mineral density, *BMC* bone mineral content, *BAP* bone alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide

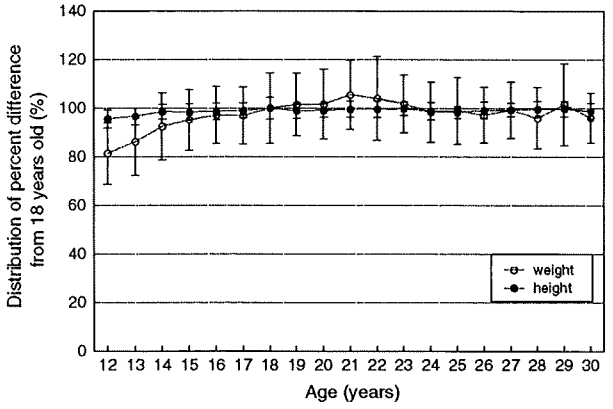

Fig. 1 Age-related distribution of skeletal parameters: height and weight. Maximum mean height was 159.8 cm at age 18. Height remained almost constant thereafter. Maximum mean weight was 55.3 kg at age 21. Weight continued to increase even after height stopped increasing. Means at each age were divided by the mean at age 18

The age-related distribution of blood markers is shown in Fig. 3. Serum calcium was constant at 9.6 ± 0.4 mg/dL between ages 12 and 30. Serum phosphorus gradually decreased from age 12 to 18, with a difference of 15.1%, which, however, remained constant thereafter. In regard to the serum bone metabolic markers BAP and NTX, there were differences of 273.8 and 208.5%, respectively, from 12 to 18 years old, with these values remaining almost constant thereafter.

Correlation between BMD, BMC, bone area and other parameters

In the age group ranging from 12 to 18 years old, where an age-related difference was observed, we analyzed the parameters examined for correlation. Results of the statistical analyses of these parameters performed every 2 years are shown in Tables 2 and 3. At age 12, age at menarche, height, body weight, serum phosphorus, BAP, and NTX were significantly correlated with lumbar spine BMD. As the subjects grew older, there was less correlation between these parameters. The same was true with the total hip BMD. On the other hand, these parameters were significantly correlated with both lumbar spine BMC and total hip BMC from ages 12 to 18. Height and weight were significantly correlated with lumbar spine bone area, while height alone was significantly correlated with total hip bone area during the same period.

Discussion

It is reported that there are two growth spurts in BMD: 1–4 and 12–17 years [17, 18], suggesting their association with

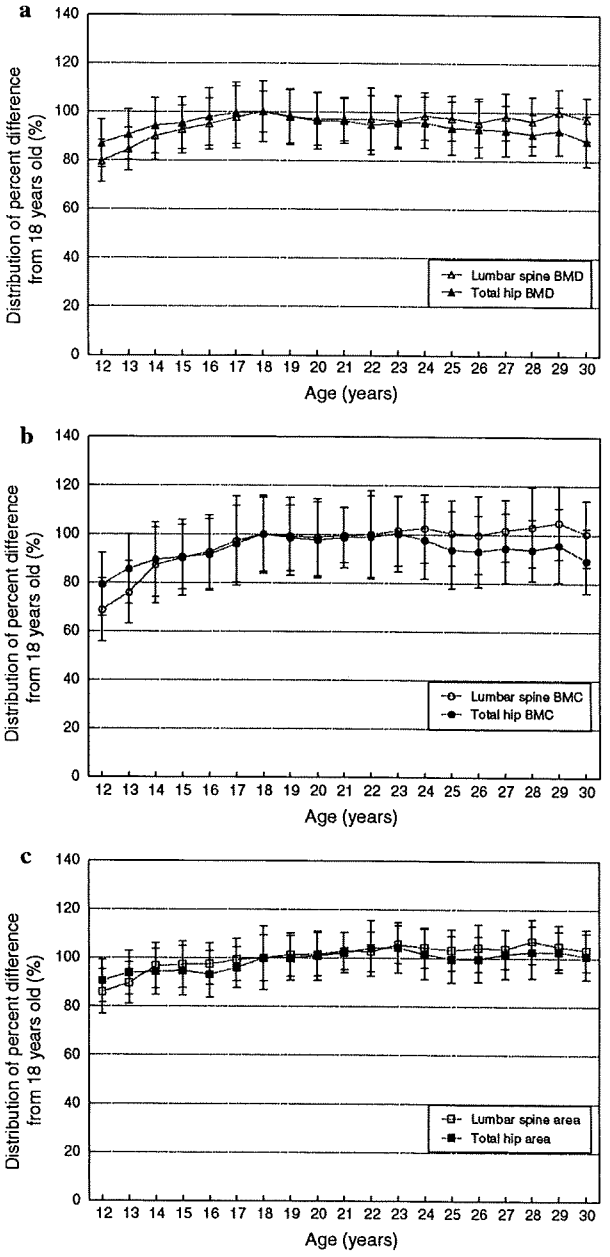

Fig. 2 Age-related distribution of BMD at the lumbar spine and total hip (**a**), BMC at the lumbar spine and total hip (**b**), bone area at the lumbar spine and total hip (**c**). Means at each age were divided by the mean at age 18. **a** Age-related distribution of BMD at the lumbar spine and total hip. Maximum mean total hip BMD was 0.934 g/cm^2 at age 18. Maximum lumbar spine BMD was 1.027 g/cm^2 at age 29, of which 99.8%, 1.025 g/cm^2, was attained at age 18. **b** Age-related distribution of BMC at the lumbar spine and total hip. Maximum total hip BMC was 29.1 g at age 18. Maximum lumbar spine BMC was 48.4 g at age 29, of which 95.2%, 44.2 g, was attained at age 18. **c** Age-related distribution of bone area at the lumbar spine and total hip. Maximum mean total hip bone area was 32.6 cm^2, of which 95.8%, 31.2 cm^2, was attained at age 18. Maximum mean lumbar spine bone area was 45.4 cm^2 at age 23, of which 94.7%, 43.0 cm^2, was attained at age 18

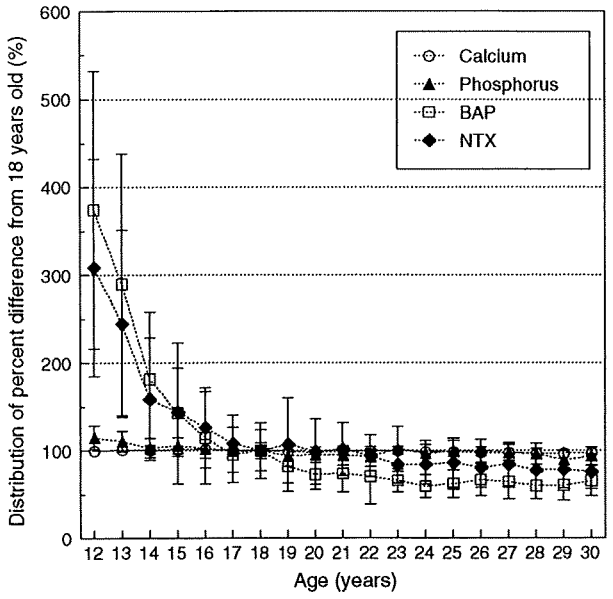

Fig 3 Age-related distribution of blood markers: serum calcium, phosphorus, BAP, and NTX. *BAP* bone alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide. Serum calcium was constant at 9.6 ± 0.4 mg/dL between the ages of 12 and 30. Serum phosphorus gradually decreased, from age 12 to 18, with a difference of 15.1%. Thereafter, it was constant. With regard to the serum bone metabolic markers BAP and NTX, there were 273.8% and 208.5% differences, respectively, from 12 to 18 years, while these levels remained almost constant thereafter. Means at each age were divided by the mean at age 18

bone formation, given that these spurts occur during the period of growth in height, body weight and development in Tanner stage [19]. There have been several hypotheses put forward about when bone mass reaches its peak. Some studies report bone mass plateauing by late adolescence [7–11], whereas others report gains, albeit small, during the third decade of life [12–16]. Many studies report bone mass reaches its peak at most sites by late adolescence [12, 15]. We selected subjects aged 12–30 years old for this study to clarify the effect of duration of exposure to estrogen after menarche in the subjects in whom the mean age at menarche was shown to be 12. While there are reports that suggest gains after the 20s, we defined the upper limit as age 30, so that the study results would not have to be adjusted for age-related differences which would make our analysis complex. We included birth weight and gestational age at birth for analysis of their potential association with genetic factors. We also included height and body weight, assuming that increases in height and body weight might affect BMC and bone area. We also postulated that there existed a relationship between calcium and bone metabolic markers.

Our study showed that BMD peaked at age 18 at both the lumber spine and total hip, which was consistent with

Table 2 Age-related correlation between lumbar spine BMD, BMC, bone area and other parameters

	Age group			
	12 years old	14 years old	16 years old	18 years old
BMD				
Birth weight	−0.053	0.022	0.121	−0.103
Gest. age at birth	0.163	0.071	0.154	−0.101
Age at menarche	−0.315**	−0.308**	−0.156	0.044
Height	0.363***	0.312**	0.292**	0.057
Weight	0.555***	0.504***	0.430***	0.479
Calcium	0.118	0.145	−0.080	0.334
Phosphorus	−0.416***	−0.051	−0.016	−0.069
BAP	−0.454***	−0.293**	−0.031	−0.475
NTX	−0.455***	−0.274**	−0.203*	−0.043
BMC				
Birth weight	−0.013	0.027	0.142	−0.147
Gest. age at birth	0.201*	0.055	−0.028	−0.620*
Age at menarche	−0.219	−0.310**	−0.062	0.155
Height	0.594***	0.526***	0.543***	0.589*
Weight	0.614***	0.606***	0.493***	0.736**
Calcium	0.161	0.202*	−0.138	0.024
Phosphorus	−0.384***	−0.133	−0.051	0.155
BAP	−0.489***	−0.339***	0.028	−0.168
NTX	−0.494***	−0.295**	−0.053	−0.002
Bone area				
Birth weight	0.061	0.004	0.111	0.187
Gest. age at birth	0.193*	0.005	−0.159	−0.701**
Age at menarche	−0.140	−0.184	0.055	0.195
Height	0.681***	0.593***	0.677***	0.811***
Weight	0.538***	0.495***	0.414***	0.657**
Calcium	0.147	0.158	−0.199	−0.223
Phosphorus	−0.296***	−0.194*	−0.075	0.094
BAP	−0.427***	−0.247***	0.096	0.096
NTX	−0.403***	−0.236*	0.130	0.013

Spearman's rank-order correlation coefficient

BMD bone mineral density, *BMC* bone mineral content, *BAP* bone alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide, *Gest.* age at birth, gestational age at birth

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

the reports of Matkovic et al. [12] and Nguyen et al. [15]. More recently, Nordstorm et al. [20] conducted an eight-year longitudinal study of BMD as assessed by DXA in young adult men, 17–25 years of age, and found that, after bone mass peaked at age 19 in the subjects, there was a progressive decrease in BMD of up to 1.5% per year in the hip, while the peak BMD was maintained as measured at the lumbar spine and the total body. Our study revealed similar results showing that BMD began to decrease at age 18, consistent with a published report that BMD peaks at

Table 3 Age-related correlation between total hip BMD, BMC, bone area and other parameters

	Age group			
	12 years old	14 years old	16 years old	18 years old
BMD				
Birth weight	0.044	0.030	0.180	0.011
Gest. age at birth	0.002	0.009	0.299**	−0.130
Age at menarche	−0.050	−0.170	−0.086	−0.251
Height	0.301**	0.286**	0.177	0.000
Weight	0.559***	0.442***	0.353**	0.496
Calcium	0.224*	0.219*	−0.247*	0.044
Phosphorus	−0.276**	−0.057	0.145	0.096
BAP	−0.327***	−0.297**	−0.029	−0.521*
NTX	−0.329***	−0.173	−0.048	−0.316
BMC				
Birth weight	0.113	0.126	0.104	0.108
Gest. age at birth	0.083	−0.010	0.075	−0.488
Age at menarche	0.105	−0.023	0.010	0.361
Height	0.603***	0.518***	0.444***	0.589*
Weight	0.676***	0.594***	0.328**	0.696**
Calcium	0.063	0.172	−0.099	0.162
Phosphorus	−0.188*	−0.074	0.029	0.115
BAP	−0.236*	−0.128	0.091	−0.254
NTX	−0.260**	−0.119	0.151	−0.125
Bone area				
Birth weight	0.165	0.170	0.038	0.125
Gest. age at birth	0.209*	−0.054	−0.180	−0.620*
Age at menarche	0.154	0.131	0.181	0.576*
Height	0.616***	0.511***	0.508***	0.829***
Weight	0.442***	0.459***	0.124	0.507
Calcium	−0.097	0.034	0.137	0.049
Phosphorus	0.018	−0.066	−0.098	0.197
BAP	0.005	0.103	0.222*	0.239
NTX	−0.022	−0.054	0.235*	0.131

Spearman's rank-order correlation coefficient

BMD bone mineral density, *BMC* bone mineral content, *BAP* bone alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide, *Gest.* age at birth, gestational age at birth

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

the hip before age 20, followed by the whole body in 6–10 years [21] and another demonstrating that BMD peaks at the femoral neck before the lumbar spine [22]. While there are studies reporting that the timing of peak BMD is not clear [23, 24], we believe our study showed that BMD peaks before age 18, at least in the total hip, given that the mean at age 18, 0.934 g/cm^2, was shown to be the maximum. As for the reference value in Japan, a report published in 2000 defined the young adult mean BMD at the total hip as 0.863 ± 0.110 g/cm^2, which represents the mean total hip BMD in subjects aged 19–39 years old [25], using the same QDR machine for measurements as we used in our study. However, the PBM value was shown to be higher at 0.934 g/cm^2 in our study than the Japanese reference value for the young adult mean. Although this may reflect differences in the cohorts as well as in the concept of PBM and the young adult mean, it is worth noting that the mean was shown to be higher in our study than in the previous study.

On the other hand, as for the lumbar spine, the peak BMD was shown to be 1.027 g/cm^2 at age 29. As Heaney et al. [21] and Neville et al. [22] reported, bone mass peaks later at the lumbar spine than at the total hip. Although not representing the peak value, the young adult mean in the lumbar spine, the mean in individuals aged 20–40 years, was reported to be 1.011 ± 0.119 g/cm^2 in 1998 [26]. As compared with our peak BMD value, 1.027 g/cm^2, the previously determined young adult mean was low as was the mean at the total hip, suggesting that the BMD in the Japanese population is increasing, given that there are reports showing that more than 95% of BMD at all sites of the body is attained by age 20. In our study, at age 18, the BMD value accounted for 99.8% of the peak value to be attained at age 29. Thus, we consider it reasonable to conclude that peak BMD is attained at age 18, consistent with the previous reports demonstrating that at least 90% of the peak BMD is attained, regardless of body sites, by the end of adolescence [13, 27]. Of note, there is a report [12] showing that BMC continues to increase in adults after BMD attains its peak with the increase after age 18 being greater in BMC than BMD and that total hip BMC peaks at age 18 with no increase occurring after that. In our study, 95.2% of the peak BMC was attained in the lumbar spine at age 18, while 99.8% of the peak BMC was attained in the total hip at age 18. There have been no reports regarding the peak time in bone area. In our study, bone area peaked at age 23 at both the lumbar spine and total hip.

In this study, we analyzed relevant parameters for association with BMD, BMC, and bone area. During the period of change in BMD, height and body weight were significantly correlated with BMD, BMC, and bone area at both the lumbar spine and total hip. While it is hardly possible to intervene for height, it appears possible to intervene for body weight through lifestyle modifications. However, there is a report [28] showing that weight gain in late adolescence might inhibit periosteal expansion, thus presenting an obstacle to enhancing bone strength. Thus, hip structure analysis may be necessary. There is no report on the age-related distribution of bone metabolic markers from adolescence to age 30. In this regard, our results are consistent with those of the report by Yilmaz et al. [29] on Thai women 11–15 years, showing that bone metabolic markers decrease as the Tanner stage progresses.

Our study showed that the PBM was attained at age 18 in women in Tokyo, Japan. It also suggested the importance of intervention in these women by age 18 by using total hip BMD as an index for such intervention, as well as the importance of weight control in these individuals.

In conclusion, in light of the findings obtained on the skeletal parameters, the impact of duration of exposure to estrogen after menarche, bone and calcium metabolism, our study reveals that BMD peaks in late adolescence, which appears to be supported by the fact that the rapid decrease in BAP and NTX ceases by that age. Moreover, our results show that BMD in the total hip begins to decrease at age 18 after peaking, whereas lumbar spine BMD increases by about 5% during the 20s after age 18. We therefore consider it necessary to intervene by age 18 using total hip BMD as an index in order to increase PBM. Our results suggest an optimal timing for intervention for bone mass as well as an index for such intervention.

Acknowledgments We would like to thank Dr. Naohito Yamaguchi, professor and chair of the Department of Hygiene and Public Health II, for his informative discussion of the statistics and epidemiology. We would also like to thank Dr. Yuko Miyabara, Department of Obstetrics and Gynecology, for her contribution to the study. This study was financially supported by a grant from the Japan Osteoporosis Foundation.

References

1. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE (1989) Survival experience of aged hip fracture patients. Am J Public Health 79:274–278
2. Roos LL, Fisher ES, Sharp SM, Newhouse JP, Anderson G, Bubolz TA (1990) Postsurgical mortality in Manitoba and New England. JAMA 263:2453–2458
3. Ilich JZ, Badenhop NE, Matkovic V (1996) Primary prevention of osteoporosis: pediatric approach to disease of the elderly. Womens Health Issues 6:194–203
4. Carrié Fässler AL, Bonjour JP (1995) Osteoporosis as a pediatric problem. Pediatr Clin North Am 42:811–824
5. Hansen MA, Overgaard K, Riis BJ, Christiansen C (1991) Role of peak bone mass and bone loss in postmenopausal osteoporosis: 12 year study. BMJ 303:961–964
6. Bachrach LK (2001) Acquisition of optimal bone mass in childhood and adolescence. Trends Endocrinol Metab 12:22–28
7. Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, Bonjour JP (1992) Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J Clin Endocrinol Metab 75:1060–1065
8. Kroger H, Kotaniemi A, Kroger L, Alhava E (1993) Development of bone mass and bone density of the spine and femoral neck—a prospective study of 65 children and adolescents. Bone Miner 23:171–182
9. Lu PW, Briody JN, Ogle GD, Morley K, Humphries IR, Allen J, Howman-Giles R, Sillence D, Cowell CT (1994) Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross-sectional and longitudinal study. J Bone Miner Res 9:1451–1458
10. Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R (1999) Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. J Clin Endocrinol Metab 84:4702–4712
11. Kemper H (2000) Skeletal development during childhood and adolescence and the effects of physical activity. Pediatr Exerc Sci 12:198–216
12. Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, Andon MB, Smith KT, Heaney RP (1994) Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. J Clin Invest 93:799–808
13. Teegarden D, Proulx WR, Martin BR, Zhao J, McCabe GP, Lyle RM, Peacock M, Slemenda C, Johnston CC, Weaver CM (1995) Peak bone mass in young women. J Bone Miner Res 10:711–715
14. Armstrong DW 3rd, Shakir KM, Drake AJ 3rd (2000) Dual X-ray absorptiometry total body bone mineral content and bone mineral density in 18- to 22-year-old Caucasian men. Bone 27:835–839
15. Nguyen TV, Maynard LM, Towne B, Roche AF, Wisemandle W, Li J, Guo SS, Chumlea WC, Siervogel RM (2001) Sex differences in bone mass acquisition during growth: the Fels Longitudinal Study. J Clin Densitom 4:147–157
16. van der Sluis IM, de Ridder MA, Boot AM, Krenning EP, de Muinck Keizer-Schrama SM (2002) Reference data for bone density and body composition measured with dual energy x ray absorptiometry in white children and young adults. Arch Dis Child 87:341–347 discussion 341-347
17. Southard RN, Morris JD, Mahan JD, Hayes JR, Torch MA, Sommer A, Zipf WB (1991) Bone mass in healthy children: measurement with quantitative DXA. Radiology 179:735–738
18. Eastell R, Lambert H (2002) Diet and healthy bones. Calcif Tissue Int 70:400–404
19. Boot AM, de Ridder MA, Pols HA, Krenning EP, de Muinck Keizer-Schrama SM (1997) Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. J Clin Endocrinol Metab 82:57–62
20. Nordstrom P, Neovius M, Nordstrom A (2007) Early and rapid bone mineral density loss of the proximal femur in men. J Clin Endocrinol Metab 92:1902–1908
21. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C (2000) Peak bone mass. Osteoporos Int 11:985–1009
22. Neville CE, Robson PJ, Murray LJ, Strain JJ, Twisk J, Gallagher AM, McGuinness M, Cran GW, Ralston SH, Boreham CA (2002) The effect of nutrient intake on bone mineral status in young adults: the Northern Ireland young hearts project. Calcif Tissue Int 70:89–98
23. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB (1992) Bone gain in young adult women. JAMA 268:2403–2408
24. Teegarden D, Proulx WR, Kern M, Sedlock D, Weaver CM, Johnston CC, Lyle RM (1996) Previous physical activity relates to bone mineral measures in young women. Med Sci Sports Exerc 28:105–113
25. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
26. Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, Nakamura T, Kushida K, Tanaka H, Ikai T, Oh-Hayashi Y (1998) Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 16:139–150

27. Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R (1991) Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab 73:555–563
28. Petit MA, Beck TJ, Hughes JM, Lin HM, Bentley C, Lloyd T (2008) Proximal femur mechanical adaptation to weight gain in late adolescence: a six-year longitudinal study. J Bone Miner Res 23:180–188
29. Yilmaz D, Ersoy B, Bilgin E, Gumuser G, Onur E, Pinar ED (2005) Bone mineral density in girls and boys at different pubertal stages: relation with gonadal steroids, bone formation markers, and growth parameters. J Bone Miner Metab 23:476–482

生涯教育

日本医師会生涯教育講座

開催日：平成21年4月9日（木）　共催　東京都医師会
会　場：新宿明治安田生命ホール　万有製薬株式会社

テーマ「女性の健康支援としてのメタボリックシンドローム対策」

座　長　東京都医師会理事　相馬正義

1．産婦人科で果たす女性のメタボリックシンドローム対策

東京女子医科大学産婦人科学教室主任教授　太田博明

1．はじめに

わが国の女性は20年余に亘り、世界一の長寿をほこっているが、それは生命量としてのものであって、必ずしも健康長寿、すなわち生命の質が十分に獲得されているものではない[1]。特に、偏食・過食・運動不足など昨今の生活習慣の揺るぎから代謝性疾患を含む生活習慣病が悪性腫瘍とともに生活の質や生命予後を脅かす重大疾患[2,3]となっており、2008年4月から国を挙げてのメタボリックシンドローム（metabolic syndrome：Mets）対策が施策されている。

少子高齢化社会において、産婦人科では生涯に亘る女性の健康支援を標榜し、社会的ニーズに対応している。このような中、若年女性ではやせが問題となっているが、閉経後女性では閉経によるエストロゲン分泌の低下を契機に閉経後期間とともに内臓脂肪の蓄積が増加し、BMI 25以上の肥満者の割合が年々増加し、ひいてはMetsが問題となっている。

女性のMetsもその持続により、動脈硬化を呈することが判明しており、心血管系イベントへの進展が危惧される。一方、動脈硬化と骨粗鬆症は相互に疾患関連性が認められている。加えて、これらの終末像である心血管系イベントや骨粗鬆症性骨折が介護や寝たきりの2大疾病要因であるので、女性の健康支援として、Mets対策は今や最重要課題となっている。

動脈硬化と骨粗鬆症との間には炎症を背景とした酸化ストレスが想定されているが、動脈硬化の基盤の1つとなるMetsにおける糖代謝や脂質代

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謝は骨代謝と密接に関連することが示されており、骨粗鬆症における骨密度の低下や骨折リスクの増大に影響を与える可能性は高い。しかしながら、Metsが骨代謝に与える影響や、これらに共通した介在因子については明らかになっていない。

そこで、産婦人科で果たしてきた女性に対するMets対策の1例として、われわれが取り組んでいる動脈硬化と骨粗鬆症予防を視野に入れた骨・脂質・血管の健康を守るための研究について記載する。

2．中高年ボランティア女性を対象とした最近の我々の研究から

(1)目的：中高年女性における栄養摂取および身体活動などの生活習慣とMetsとの傾きの状況を確認し、各種測定値からその指標となるものを見出す。またそれによる新しい知見の発見やそれを支援するデータベースの開発を行うこと、さらに疾病に罹患する前の早い段階、すなわち、未病レベルにて疾病の予防を行うことを目的とする。

(2)対象および方法：40～80歳の健常ボランティア女性を対象とし、予め文書による同意を得た221名に対して調査・研究を行った。対象者の背景情報を質問票により回答を得た後、身長・体重・血圧・ウェスト周囲径を実測した。また採血により、脂質代謝（TC, HDL-C, TG)、糖代謝（FBS, HbA1c)、骨代謝（ucOC)、アディポネクチン、hsCRP、ホモシステイン、ペントシジン等を含む130項目の血中各ファクターを測定した。

DHQ (self-administered Diet History Questionnaire)[4,5]による栄養調査およびJALSPAQ (self-administered Japan Arterioscleorosis Longitudinal Study Physical Activity Questionnaire)[6,7]による身体活動量調査を行った。その後、腰椎骨密度をQDR-4500を用いたDXA法により、また臓器脂肪面積（Visceral Fat Area : VFA）をImpedance法を用いた体成分析法であるIN BODYで各々測定し、各測定値を解析した。

表1　基本背景データ

		例数	Mean	SD	基準値
年齢	(歳)	221	58.6	9.0	
身長	(cm)	220	155.8	5.5	
体重	(kg)	221	54.7	8.6	
BMI		220	22.5	3.4	18.5～25
腹囲	(cm)	221	79.8	9.6	<90
sBP	(mmHg)	221	111.5	16.2	<130
dBP	(mmHg)	221	69.9	9.9	<85
BMD	(g/cm^2)	219	0.9	0.2	80%YAM
T-BMD	1	219	−0.9	1.4	<−2.5
Z-BMD		219	0.5	1.1	
rPWV	(cm/s)	221	1389.7	254.1	<1400
lPWV	(cm/s)	221	1411.1	308.3	<1400
内臓脂肪面積	(cm^2)	221	84.7	27.9	<100
体脂肪率	(%)	221	29.5	7.5	<30

平均的に見るとMetsでも動脈硬化でも骨粗鬆症でもない

(3)結果：基本背景データを表1に示すが、年齢は58.6±9.0（mean±SD）歳であり、ウェスト周囲径は79.8±9.6cm、血圧は111.5±16.2/69.9±9.9mmHg、腰椎骨密度は0.900±0.200g/cm^2、VFAは84.7±27.9 cm^2、体脂肪率は29.5±7.5％であり、平均的に見るとMetsでも、動脈硬化でも、また骨粗鬆症でもない健常者が対象であった。

血液検査データを表2に示すが、TCに関しては228.3±37.6mg/dLとやや基準値よりも高値であるが、TGおよびHDL-Cが基準値内に留まるものであり、FBSは91.1±12.5mg/dL、HbA1cも5.2±0.5％にて糖代謝は基準値内であり、骨代謝のucOCも3.7±2.6ng/mlで、いずれも基準値内であった。またアディポネクチンも11.3±5.7 μg/mlと基準値を上回る、十分に分泌がなされている集団であった。hsCRPも0.1±0.1mg/dLと基準値内で、ホモシステインも7.4±1.6nmol/ml、ペントシジンも140.5±39.5pmol/mlとVit B_6関連および葉酸値なども含め、いずれも基準

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表2　血液検査データ

		例数	Mean	SD	基準値
Ca	(mg/dL)	221	9.8	0.4	8.4-10.3
P	(mg/dL)	221	3.9	0.7	2.5-4.3
TG	(mg/dL)	221	96.7	51.3	30-150
TC	(mg/dL)	221	228.3	37.6	130-220
HDL-C	(mg/dL)	221	71.5	17.0	40-69
空腹時血糖値	(mg/dL)	221	91.1	12.5	65-105
HbA1c	(%)	221	5.2	0.5	4.3-5.8
CK-MB	(U/L)	221	3.8	1.8	≦5.2
ホモシステイン	(nmol/ml)	221	7.4	1.6	3.7-13.5
ペントシジン	(pmol/ml)	221	140.5	39.5	91.5-431
B6PAM	(ng/ml)	221	0.2	0.1	<0.6
B6PAL	(ng/ml)	221	24.7	98.4	4.0-19.0
B6PIN	(ng/ml)	221	3.0	0.4	<3.0
葉酸	(ng/ml)	221	12.6	4.1	4.4-13.7
アディポネクチン	(μg/ml)	221	11.3	5.7	5-10
ucOC	(ng/ml)	221	3.7	2.6	<4.5
hsCRP	(mg/dL)	221	0.1	0.1	<0.3
Apo A1	(mg/dL)	221	168.9	26.7	126-165
Apo B	(mg/dL)	221	98.5	24.4	66-101

値内にて高値を示す集団ではなかった。

次にこの対象者の1日あたりの栄養摂取データを表3に示す。40～70歳のわが国の平均値と比べて、摂取エネルギー量は僅かに多く、三大栄養素の摂取量としては脂肪のみやや多く、Ca摂取量は524±226.2mg/日と平均値を上回るが、SD値も大きいので、摂取量の個人差が大きいことが示されている。ビタミンのB_1、B_2、B_6、B_{12}はいずれもやや低く、葉酸、VDおよびVKの摂取量はやや多かった。

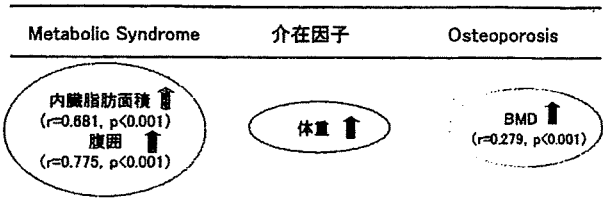
Mets診断基準項目であるウェスト周囲径90cm以上は33名（15.8％）、TG 150mg/dL以上は29名（13.1％）、HDL-C 40mg/dL未満は1名（0.5％）、FBS 110mg/dL以上は13名（5.9％）、血圧130/85mmHg以上は29％（13.1％）存在した。しかし、Metsの診断基準を充たすものは5名（2.3％）であった。また、原発性骨粗鬆症の診断基準により、骨粗鬆症は26名（11.9％）、骨量減少80名（39.3％）、正常107名（48.8％）であった。骨粗鬆症群および骨量減少群は正常群と比較し、低HDL-C、高ucOC、高PWVおよび低体重であった。一方、PWVの基準値1,400cm/sec以上を示すものは88名（39.8％）であった。

表3　1日あたりの栄養摂取データ

		例数	Mean	SD	40-70歳代の平均値
摂取重量	(g)	182	2867.0	898.9	ND
摂取エネルギー	(kcal)	182	1805.2	465.3	1738
蛋白質	(g)	182	64.1	20.1	87.35
脂肪	(g)	182	54.3	20.9	48.4
炭水化物	(g)	182	249.4	63.9	251
Ca	(mg)	182	524.0	226.2	474.5
P	(mg)	182	1013.1	327.9	976.5
K	(mg)	182	2468.6	870.5	2488.5
n-3	(g)	182	2.5	1.02	ND
n-6	(g)	182	10.1	3.6	ND
Cholesterol	(mg)	182	265.0	144.0	294
VB1	(mg)	182	0.9	0.3	1.56
VB2	(mg)	182	1.3	0.4	1.47
VB6	(mg)	182	1.2	0.5	1.98
VB12	(μg)	182	7.8	5.1	7.1
葉酸	(μg)	182	339.2	135.1	332
VD	(μg)	182	8.7	4.7	8.28
VK	(μg)	182	307.4	171.5	256

この基準値の高低で比較すると、血圧と身長における有意差はさることながら、FBS、VFA、年齢が有意に高値を、骨密度は有意な低値を認めた。

Metsおよび骨粗鬆症の指標であるVFAおよびBMDの両者に関与するものとして、年齢、体重、BMI、アディポネクチン、HDL-C、Apo A_1、PWVの7因子が抽出された。しかし、Metsや骨粗鬆症が進行して心血管系イベント、糖尿病合併症および骨折を併発しないとホモシステイン、ペントシジンは有意な変動を認めなかった。また、体格指標としての体重がBMDおよびVFAと有意な正相関（r＝0.279、p＜0.001およびr＝0.681、p＜0.001）を認め（図1）、さらにHDL-CもBMDおよびVFAと有意な負相関（r＝－0.159、p＝0.021およびr＝－0.421、p＜0.001）を認めた



体重があると内臓脂肪面積と腹囲の増大とともに
骨密度の高値につながる

体重はMetsに負に，また骨密度には正に作用する

図1　メタボリックシンドロームと骨粗鬆症との疾患関連性(1)

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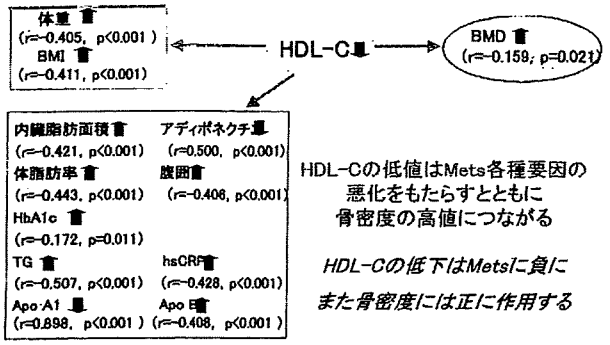

図2　メタボリックシンドロームと骨粗鬆症との疾患関連性(5)

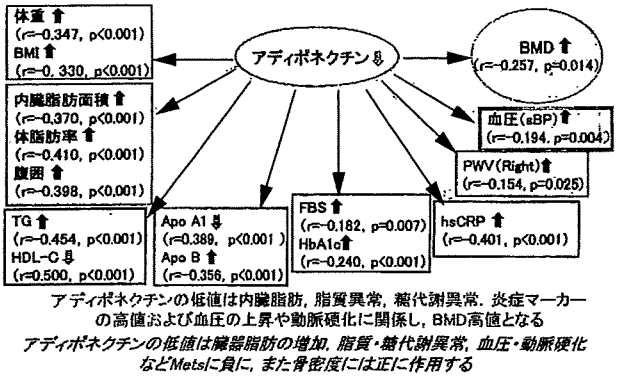

図3　メタボリックシンドロームと骨粗鬆症との疾患関連性(3)

（図2）。加えて、アディポネクチンもBMDおよびVFAと有意な負相関（r＝－0.257、p＝0.014および r＝－0.370、p＜0.001）を呈した（図3）。しかし、PWVはBMDとは有意な負相関（r＝－0.281、p＝0.007）を、またVFAとは有意な正相関（r＝0.427、p＜0.001）を各々呈した（図4）。

(4)考察

①　体重の骨密度およびVFAに対する関与

BMDの維持には重力による負荷が必要であり、寝たきりは骨粗鬆症の発症を惹起する。逆に肥満では骨にかかる重力負荷が増大するため、骨量は増加すると考えられる。実際に高齢者を対象としたフラミンガム研究では、体重やBMIと高い相関を示すことが報告[9]されている。肥

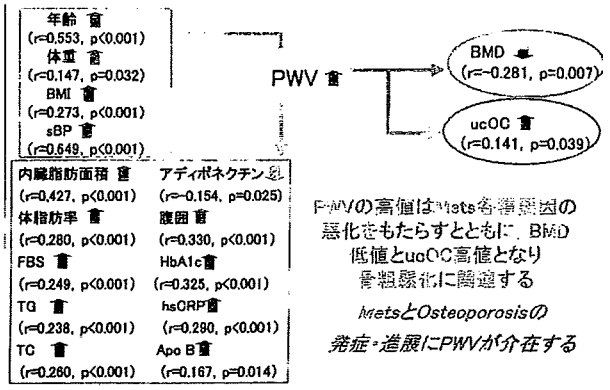

図4　メタボリックシンドロームと骨粗鬆症との疾患関連性(6)

満は高い骨密度のため低い骨折率と関連[9]し、肥満と一致する過度の脂肪量は骨格に対する機械的負荷を誘発する[8]。また、中高年女性や男性を対象とした検討でも体重の増加に従って骨量が増加するという同様の成績が多く得られている。さらにBMIの増加に伴い骨吸収マーカーおよび骨形成マーカーはいずれも低下することから、肥満では骨吸収が低下する[10,11]ことで、骨量が増加すると考えられる。

一方で、過体重、すなわち肥満では一般に脂肪量が増加することから、脂肪の増加こそが肥満における骨量増加の誘因であると推察されてきた。他方、脂肪組織を構成する白色および褐色脂肪細胞は、骨芽細胞や軟骨細胞・筋芽細胞と同様に中胚葉由来の細胞を起源とする。実際に、老年期の骨粗鬆症において骨髄中の脂肪細胞が増加し、骨芽細胞が減少する[12]こと、幼年期における骨折は肥満のリスクを高めること[13]などからも脂肪細胞と骨代謝との関連性が示されている。そのため、これらの細胞分化方向を制御する分子機構の解明が、Metsの治療法における鍵の1つであると考えられる。

近年、脂肪細胞や骨芽細胞分化を制御する因子群が多数報告されているが、興味深いことにこれらの因子は相互の分化を制御する例が多い。

特に脂肪細胞分化促進因子である核内レセプター型転写因子PPAR-γは同時に骨芽細胞分化抑制機能を有することが知られ、骨代謝におけるPPAR-γ機能の重要性が示唆されている。すなわち、本来脂肪細胞分化制御因子として報告されたPPAR-γであるが、骨髄間葉系幹細胞においてもPPAR-γリガンド（チアゾリジン誘導体）が脂肪細胞を促進[14]し、骨芽細胞分化を抑制することから、PPAR-γが前駆脂肪細胞から脂肪細胞のみならず、間葉系幹細胞からの分化の方向性を規定する因子であることが見出されている。

また、PPAR-γ欠損ヘテロマウスの解析からもPPAR-γが骨量を負に調節する[15]ことが支持されているが、近年破骨細胞特異的PPAR-γ KOマウスの結果から、PPAR-γがC-FOSを標的遺伝子として破骨細胞分化誘導に機能することが示唆された[16]ため、骨代謝全体におけるPPAR-γの作用点は骨芽細胞と破骨細胞のどちらが重要であるかは今後の課題となっている。

これらのことから、過体重すなわち肥満による脂肪細胞の活性化はPPAR-γによってなされるが、一方でPPAR-γは骨代謝に抑制的に作用するため、骨密度に負に傾く。今回の本研究結果とは逆のことが想定される。このことは2型糖尿病における骨量増加および骨折増加から説明できるかもしれない[17,18,19]とされている。すなわち、過体重から骨密度は増加するが、PPAR-γによって骨代謝が抑制されるので、骨質の劣化につながり、易骨折性を呈する可能性がある。従って過体重であって、インスリン欠乏状態、高血糖状態、それに糖尿病に伴う合併症がある。さらに絶対的・相対的インスリン欠乏が骨芽細胞の機能や数を低下させ、持続は高血糖により骨芽細胞機能のさらなる低下が招来され、骨折の危険性がより高くなるものと思われる。

② HDL-Cの骨密度およびVFAに対する関与

脂肪組織蓄積に並行して出現する高TG血症、低HDL-C血症の骨に対する影響は現在のところ明らかではない。本研究ではTG高値は骨密度との相関はなく、HDL-C低値のみ骨密度との相関を認めている。またTG高値およびHDL-C低値はVFAと正の相関を予想通り認めている。HDL-C低値と骨密度高値との関係については、いくつかの報告があるが、現時点では意見の一致をみていない。すなわち、Hsuら[20]の報告によると、中国人を対象とした7,137人の男性、4,585人の閉経前女性、2,248人の閉経後女性において、年齢、身長、% fat、身体活動性、喫煙、飲酒量等で補正後、男性、閉経前女性、閉経後女性いずれの群においてもTGは全身BMCに対して有意な負相関を示したが、HDL-Cは有意な相関を示さなかったという。さらに70歳以上の中国人男性368人を対象に、年齢、身長、体重、% fat等で補正後、TGは超音波で測定した踵骨骨密度とは正の相関を示し、HDL-Cは有意な相関を示さなかった[21]。白人閉経後女性1,176人を対象としたBaggerらの報告[22]では、年齢、閉経後年数、BMI、% fat、喫煙、身体活動性等で補正後、TGとHDL-Cのいずれも大腿骨頸部および腰椎骨密度と有意な相関を示さなかった。しかし、椎体骨折群では非骨折群に比較して有意にTGが低値であったという。

一方、日本人閉経後女性214人を対象とした研究[23]では、年齢、閉経後年数、BMI、% fatで補正後、TGは腰椎、大腿骨頸部、橈骨のいずれの骨密度とも有意な相関がなかったが、HDL-Cは腰椎および橈骨の骨密度と有意な正

相関を示し、本研究結果と一致していた。さらにYamaguchi[23]らはBaggerら[22]と同様に、椎体骨折群では非骨折群に比較して有意にTGが低値であり、ロジスティック解析ではTGがISD上昇するごとに、椎体骨折の危険率は0.51倍と有意に低下したという。またノルウェーの白人男女27,159人を対象としたAhmedら[24]は、肥満、高TG血症、低HDL-C血症、高血圧のMetsの各因子が重複するほど非椎体骨折の相対危険率が低下し、3つ以上の重複では危険率が男性においては0.71倍、女性においては0.66倍低下したという。

Metsを構成する高TG血症および低HDL-C血症は、以上のごとく骨折危険率を低下させる可能性が示唆されているが、今後の検討が必要である。

③　アディポネクチンの骨密度およびVFAに対する関与

次にアディポネクチンと骨密度およびVFAとの関係に関してまとめると以下のごとくとなる。アディポネクチンの低値はVFAとウェスト周囲径の増大をもたらすと共に骨密度高値につながるが、VFAとウェスト周囲径の増大は過体重によって示される骨密度の増大に結びつくものと考えられる。アディポネクチンと骨密度との関連性を初めて報告したものはLenchikら[25]であると思われる。この報告によると、年齢、性、人種、喫煙、糖尿病状態を補正後、血清アディポネクチンは部分的骨密度（$r=-0.20$ to -0.30、all $p<0.01$）、容積測定の骨密度（$r=-0.35$ to -0.44、all $p<0.01$）および内臓脂肪量（$r=-0.30$、$p<0.01$）と負に相関したという。これらのデータはアディポネクチンが骨密度に対するVFAの保護効果を示している可能性があるという。

しかし、一方でアディポネクチンは骨密度に何の効果も発揮しなかったが、レプチンは負の効果を発揮するという報告[26]があるが、Third US National Health and Nutrition Examination Surveyによる大規模研究[27]ではレプチンと骨密度との相関は明らかにすることはできなかったという。レプチンの骨代謝における役割は研究によって骨密度と正にも負にも相関することが示されており、明らかではない[28]。また、最近のJürimäeらの研究[29]によると閉経前女性におけるアディポネクチンは骨密度値の偏位の3～12％を説明し、レプチンよりもアディポネクチンの方が骨代謝とより直接的に関係する重要なシグナルを与えている可能性があるとしている。このメカニズムとしてアディポネクチンがCOX-2を介して骨代謝効果[30]を及ぼすとされている。しかし、一方で血清アディポネクチンと骨密度とは負の関係にあり、これは閉経後女性に限ったことで、閉経前女性ではないという[28]。このことはエストロゲン補充療法を行っている閉経後女性が、行っていない閉経後女性よりも低いアディポネクチンレベルを有していることが認められ[31]、エストラジオールレベルがアディポネクチンレベルと負に相関することから示されている[32]。閉経後女性では脂肪組織がエストロゲンの主な源となり[33]、続いてBMIが低ければエストロゲンがより低く、アディポネクチンがより高くなる。またアディポネクチンはMAPKシグナル回路を介してRANKLを刺激し、OPGの発現を抑制し[34]、RANKLは骨吸収に対し、強い刺激をし、OPGはRANKL誘導される骨損失を防ぐ[35]ことから、アディポネクチンは骨吸収のRANKL回路の促進を通して骨代謝に効果を発揮する[28]のではないかという。

肥満は心血管系疾患や糖尿病を含めた多数の疾患に対しては負の影響を及ぼすにも関わらず、

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骨粗鬆症に対しては保護している[9]ようにみえる。体重とBMIがあると、骨折率は有意に低くなるという複数の報告[36,37,38,39]がある。骨密度の最も強い保護指標の1つである体重[8,40,41,42,43]は閉経後の骨密度喪失と骨代謝に対して負の相関[10,44,45,46,47,48]を示す。体重はFat MassとLean Massに依存しており、Reid[48]らによってレビューされているごとく、多くの研究ではFat Massと骨密度との有意な正相関を示してきた。しかし、脂肪代謝は異なる貯蔵庫であるため、Fat Massの分布は均質ではない。従って骨密度と骨代謝が貯蔵庫に依存する影響の可能性があるが、過去には研究されていなかった。

④　PWVの骨密度およびVFAに対する関与

脂肪組織によって主に分泌されるレプチンはFat Massと有意に相関する[49]ので、レプチンの骨格への影響がより注目されている。一方、別の脂肪特異的蛋白質であり、肥満とともに減少するアディポネクチンの骨量に対する役割については知られていない[50,51,52]。マウスにおけるアディポネクチン療法は、肝の糖新生と筋肉のTGの減少[53]となり、アディポネクチンが脂肪細胞から筋肉や肝までシグナルを運ぶということを示唆するLenechik[25]のデータでは、アディポネクチンが骨密度およびVFATとの強い負の相関性を呈している。対照的にはレプチンは骨密度と関連しなかったが、SFATやVFATおよび全体脂肪量とは有意に関連したという。アディポネクチンがレプチンよりも骨密度と強い関連性を示したという事実は興味深い。つまり、アディポネクチンが脂肪組織から骨までシグナルを運ぶかもしれないということを示唆している。アディポネクチンの特性として骨代謝調節に関与するといわれている。すなわち、アディポネクチンは破骨細胞形成を調節する2つの蛋白質であるRANKLやOPGなどのTNFのfamilyと構造類似性を有する。またアディポネクチンは破骨細胞形成に関与する転写因子であるNF-kBを抑制する[54]とともに活性化[55]するなど骨に影響を与える可能性が存在する。組換え型のアディポネクチンはプレアディポネクチンに由来する骨髄中のadipogenesisを抑制する。このことはアディポネクチンは骨髄環境に影響を及ぼす[56]ということである。

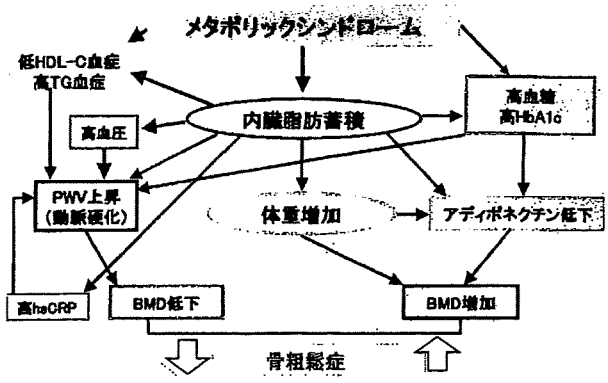

図5　メタボリックシンドロームと骨粗鬆症との疾患関連性のまとめ

PWVの骨密度およびVFAに対する関与についてはPWVは骨密度と有意な負相関、ucOCとは有意な正相関を呈する。またPWVの年齢、体格、血圧に対する因子はいずれも有意な正相関を呈する。さらにPWVの脂肪蓄積に対する関与についてはPWVと脂肪蓄積に対する各指標は有意な正相関を呈する。糖代謝に対する関与としては、PWVは糖代謝の各指標と有意な正相関を呈する。またPWVの脂質代謝および炎症マーカーに対する関与として、PWVはTGおよびhsCRPと有意な正相関を呈する。

以上から、PWVの高値はMets各種要因の悪化をもたらすとともに、骨密度低値とucOC高値となり、骨粗鬆症の発症・進展にPWVが介在することを示したものと考えている。

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3．結論

Metsと骨粗鬆症との疾患関連性をまとめると図5のごとくとなる。すなわち、Metsも内臓脂肪の蓄積だけに留まっている間は、主に体重増加とアディポネクチンの低下により、骨密度の増加を呈し、骨粗鬆症は併発しない。

しかし、内臓脂肪の蓄積を放置しておくと、高血糖、高HbA1c、高TG血症、高血糖、高CRPを呈するようになり、それらに伴って骨密度の低下を来す。すなわち、Metsの予備段階では骨密度は増加し、骨粗鬆症を併発しないが、Metsが進行して血管が硬化し、動脈硬化を来してくると骨密度は低下し、骨粗鬆化を呈するので、Metsと骨粗鬆症は併発する。従って、Metsに至らない内臓脂肪の蓄積の段階で予防策を講じれば、脂質代謝異常・糖代謝異常や高血圧の防止が可能となり、動脈硬化も抑止できる。動脈硬化が抑止できれば骨粗鬆化も招かないこととなる。すなわち、健全老化のためには健康教育、予防教育などの介入によりMetsの初期段階における内臓脂肪の蓄積を持続させないことが重要となる。これらの教育によって心血管イベントや糖尿病合併症の併発および骨粗鬆症性骨折など複数の生活習慣病の防止が可能となる筈である。このようなことから、内臓脂肪を指標とするわが国における施策である特定健診は的を射ているものと思われる。

なお、今後の課題として、内臓脂肪の蓄積がどの位の程度のものが、どの位の期間持続することにより、不可逆的な動脈硬化が形成されるのかを把 握する必要がある。この考え方は約20年のDiabetusに掲載された仮説、高血糖の記憶（hyperglycemic memory or metabolic memory）、すなわちmetabolic exposureが借金となるという考え方とほぼ同様ではないかと思われる。Metabolic exposureの程度と期間が把握できれば、健全老化対策は可能となる筈である。

文　献

1）太田博明：女性の健康寿命の延伸に対する更年期医療の役割　日本更年期医学会雑誌　2008；16(1)：74-81

2）太田博明：トータルヘルスケアとしての更年期医療－メタボリックシンドロームへの傾きにおける実態の把握と対応　産婦人科治療　2006；93(6)：723-732.

3）太田博明：更年期から取り組むトータルヘルスケアーその重要性と実践のために－　更年期と加齢のヘルスケア　2007；6(6)：32-39.

4）Sasaki S, Ushio F, Amano K, Morihara M, Todoriki O, Uehara Y, Toyooka E：Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. J Nutr Sci Vitaminol 2000；46：285-296.

5）Sasaki S, Yanagibori R, Amano K：Self-administered diet history questionnaire developed for health education：a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 1998；8：203-215.

6）Ainsworth B, Haskell W, Leon A, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr.（1993）Compendium of physical activities：classification of energy costs of human physical activities. Med Sci Sports Exerc 25：71-80.

7）Ainsworth B, Haskell W, Whitt M, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS.（2000）Compendium of physical activities：an update of activity codes and MET intensities. Med Sci Sports Exerc 32（suppl）：S49

8-516.

8) Felson DT, Zhang Y, Hannan MT, Anderson JJ. : Effects of weight and body mass index on bone mineral density in men and women : the Framingham study. J Bone Miner Res. 1993 ; 8(5) : 567-73.

9) Flegal KM, Carroll MD, Ogden CL, Johnson CL : Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002 ; 288(14) : 1723-7.

10) Ravn P, Cizza G, Bjarnason NH, Thompson D, Daley M, Wasnich RD, McClung M, Hosking D, Yates AJ, Christiansen C. : Low body mass index is an important risk factor for low bone mass and increased bone loss in early postmenopausal women. Early Postmenopausal Intervention Cohort (EPIC) study group J Bone Miner Res. 1999 ; 14 (9) : 1622-7.

11) Rogers A, Hannon RA, Eastell R. : Biochemical markers as predictors of rates of bone loss after menopause. J Bone Miner Res. 2000 ; 15(7) : 1398-404.

12) Rosen CJ, Bouxsein ML : Mechanisms of disease : is osteoporosis the obesity of bone? Nat Clin Pract Rheumatol. 2006 ; 2(1) : 35-43.

13) Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. : Bone mineral density and body composition in boys with distal forearm fractures : a dual-energy x-ray absorptiometry study. J Pediatr. 2001 ; 139(4) : 509-15.

14) Gimble JM, Robinson CE, Wu X, Kelly KA, Rodriguez BR, Kliewer SA, Lehmann JM, Morris DC. : Peroxisome proliferator-activated receptor-gamma activation by thiazolidinediones induces adipogenesis in bone marrow stromal cells. Mol Pharmacol. 1996 ; 50(5) : 1087-94.

15) Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, Terauchi Y, Harada Y, Azuma Y, Nakamura K, Kadowaki T, Kawaguchi H : PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest. 2004 ; 113(6) : 846-55.

16) Wan Y, Chong LW, Evans RM. : PPAR-gamma regulates osteoclastogenesis in mice. Nat Med. 2007 ; 13(12) : 1496-503.

17) Inaba M, Okuno S, Kumeda Y, Yamakawa T, Ishimura E, Nishizawa Y : Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus. Calcif Tissue Int. 2005 ; 76(4) : 256-60.

18) Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR ; Study of Osteoporotic Features Research Group. : Older women with diabetes have an increased risk of fracture : a prospective study. J Clin Endocrinol Metab. 2001 ; 86 (1) : 32-8.

19) Hirano Y, Kishimoto H, Hagino H, Teshima R. : The change of bone mineral density in secondary osteoporosis and vertebral fracture incidence. J Bone Miner Metab. 1999 ; 17(2) : 119-24.

20) Hsu YH, Venners SA, Terwedow HA, Feng Y, Niu T, Li Z, Laird N, Brain JD,

生　涯　教　育

Cummings SR, Bouxsein ML, Rosen CJ, Xu X. : Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am J Clin Nutr. 2006 ; 83(1) : 146-54.

21) Tang YJ, Sheu WH, Liu PH, Lee WJ, Chen YT : Positive associations of bone mineral density with body mass index, physical activity, and blood triglyceride level in men over 70 years old : a TCVGHAGE study. J Bone Miner Metab. 2007 ; 25(1) : 54-9.

22) Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB ; PERF study group : Links between cardiovascular disease and osteoporosis in postmenopausal women : serum lipids or atherosclerosis per se? Osteoporos Int. 2007 ; 18 (4) : 505-12.

23) Yamaguchi T, Sugimoto T, Yano S, Yamauchi M, Sowa H, Chen Q, Chihara K : Plasma lipids and osteoporosis in postmenopausal women. Endocr J 2002 ; 49 : 211 -217.

24) Ahmed LA, Schirmer H, Berntsen GK, Fønnebø V, Joakimsen RM : Features of the metabolic syndrome and the risk of non -vertebral fractures : the Tromsø study. Osteoporos Int. 2006 ; 17(3) : 426-32.

25) Lenchik L, Register TC, Hsu FC, Lohman K, Nicklas BJ, Freedman BI, Langefeld CD, Carr JJ, Bowden DW : Adiponectin as a novel determinant of bone mineral density and visceral fat. Bone. 2003 ; 33(4) : 646-51.

26) Kontogianni MD, Dafni UG, Routsias JG, Skopouli FN : Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women J Bone Miner Res. 2004 ; 19 (4) : 546-51.

27) Ruhl CE, Everhart JE : Relationship of serum leptin concentration with bone mineral density in the United States population. J Bone Miner Res. 2002 ; 17(10) : 1896-903.

28) Richards JB, Valdes AM, Burling K, Perks UC, Spector TD : Serum adiponectin and bone mineral density in women. J Clin Endocrinol Metab. 2007 ; 92(4) : 1517-23.

29) Jürimäe J, Jürimäe T : Adiponectin is a predictor of bone mineral density in middle -aged premenopausal women Osteoporos Int. 2007 ; 18(9) : 1253-9.

30) Oh KW, Lee WY, Rhee EJ, Baek KH, Yoon KH, Kang MI, Yun EJ, Park CY, Ihm SH, Choi MG, Yoo HJ, Park SW : The relationship between serum resistin, leptin, adiponectin, ghrelin levels and bone mineral density in middle-aged men. Clin Endocrinol (Oxf). 2005 ; 63(2) : 131-8.

31) Im JA, Lee JW, Lee HR, Lee DC : Plasma adiponectin levels in postmenopausal women with or without long-term hormone therapy. Maturitas. 2006 ; 54(1) : 65-71.

32) Szymczak J, Milewicz A, Thijssen JH, Blankenstein MA, Daroszewski J. : Concentration of sex steroids in adipose tissue after menopause. Steroids. 1998 ; 63(5-6) : 319-21.

33) Gavrila A, Chan JL, Yiannakouris N,