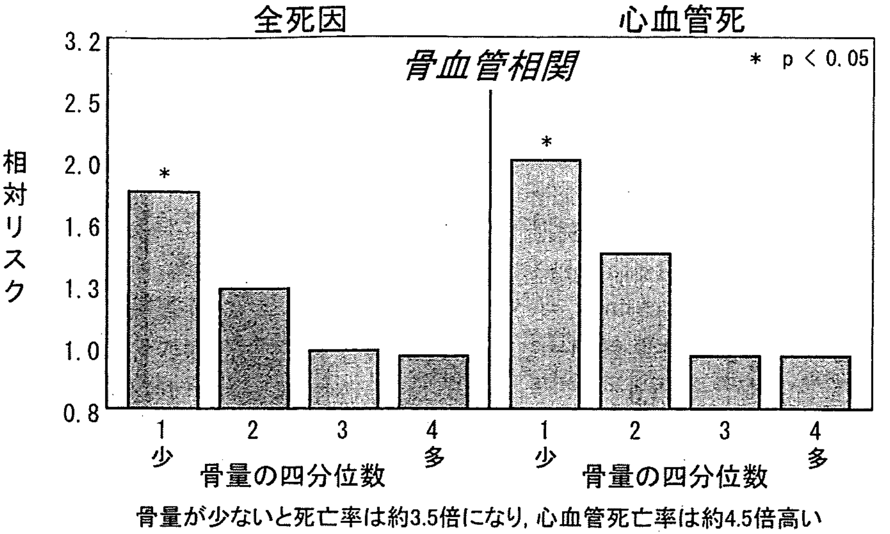
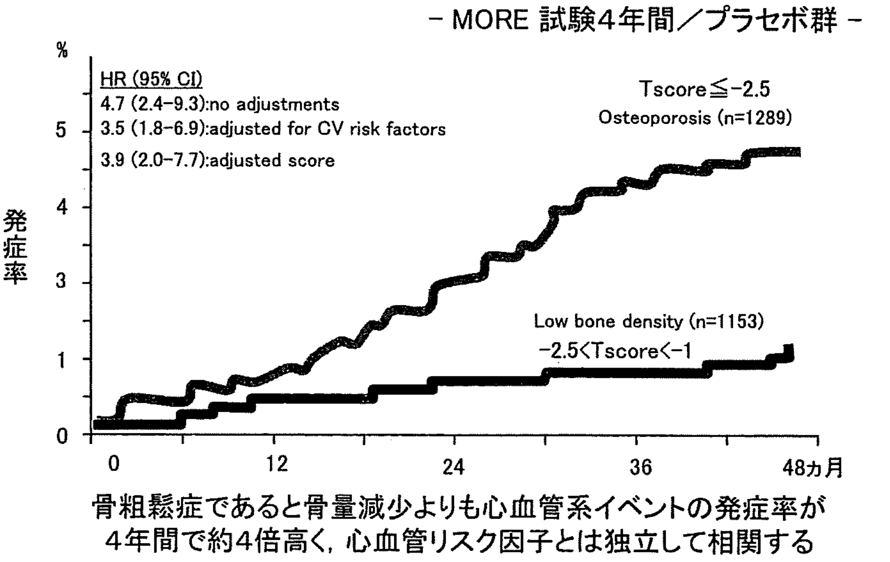


Von der Recke et al Am J Med 1999 改変

図４　閉経後女性における四分位骨量と年齢補正死亡率との関係

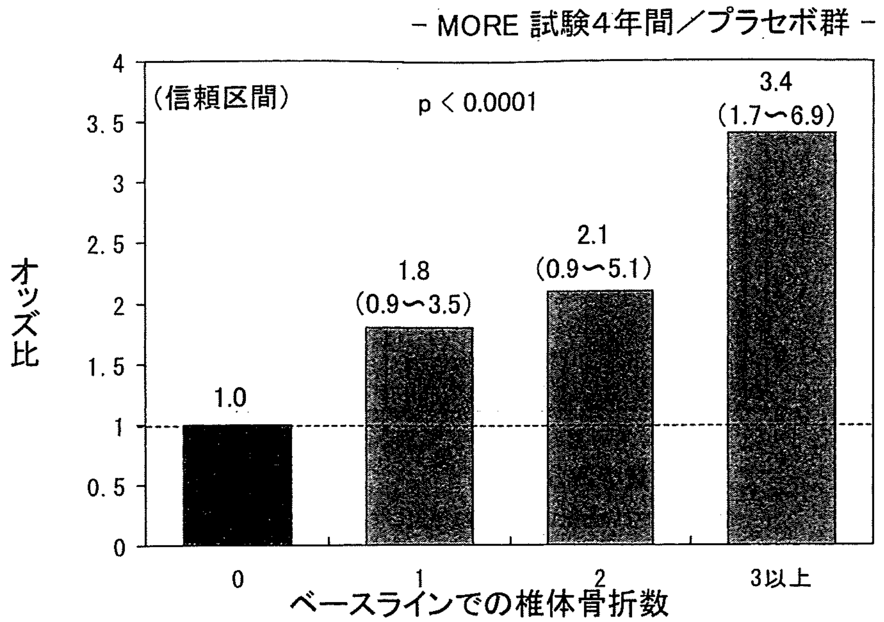


Tanko L et al JBMR 2005 改変

図５　大腿骨近位トータル骨密度と心血管系イベント発症率

番はともかく高血圧，喫煙，糖尿病があげられているが，この報告によると表４に示すごとく，ハザード比は心血管系イベントの既往が5.0, 糖尿病4.7, 次いで骨粗鬆症が3.5と続き，喫煙の2.7, 高血圧の2.6, 高脂血症の1.9よりも高いという．なお，骨粗鬆症も63.7歳を超えると3.8と上昇し，さらに70.4歳以上であると4.3となり，糖尿病の4.7に近づく．このように，骨粗鬆症であることは通常考えられている心血管リスク因子とは独立して心血管イベントと相関するといわれている．

またわれわれは骨密度である L_{24} BMDと動脈硬化の機能的指標であるPWV値との関係を検討したが，両者は有意な負の相関関係(r＝－0.320, p＝0.006)を示し，低骨密度であるとPWV値は高くなり，動脈硬化傾向にあることが判明している．さらに，同一対象に対しPWV値と骨代謝マーカーの骨型アルカリホスファターゼ（bone type alkaline phosphatase：BAP）との関係を検討したが，両者の間には有意な正相関（r＝0.248, p＝0.032）を呈した．石灰化を来した中膜の平滑筋細



椎体骨折の有無および数で心血管系疾患の発生頻度は上昇する

Tanko L et al JBMR 2005 改変

図6 椎体骨折数と心血管系疾患発生頻度

表4 骨粗鬆症と骨量減少における心血管系イベントの発症リスク（各種補正後）

項目	ハザード比	95%信頼区間	p 値
骨粗鬆症	3.5	1.8－6.9	＜ 0.001
年齢（63.7 歳〜 70.4 歳 vs 63.7 歳未満）	3.8	1.4－10.0	0.007
年齢（70.4 歳以上 vs 63.7 歳未満）	4.3	1.6－11.3	0.003
糖尿病（有/無）	4.7	1.9－12.1	0.001
心血管系イベントの既往（有/無）	5.0	2.3－10.8	＜ 0.001
高血圧（有/無）	2.6	1.5－4.5	＜ 0.001
高脂血症（有/無）	1.9	1.1－3.3	0.02
喫煙（有/無）	2.7	1.5－4.9	0.001

骨粗鬆症であることは心血管系イベントの既往および糖尿病に次いで心血管系イベントのリスクが高い

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胞では骨関連蛋白の発現を伴う形質転換が見出されているが，PWV 値の上昇に伴い，骨芽細胞機能の指標である骨形成マーカーの BAP が高値を示すことが判明した．このことは骨密度の多寡と PWV 値との関係についてのわれわれの検討でも，骨粗鬆症者のみならず，骨量減少者においてもそれぞれ PWV 値は骨密度の正常者のそれと比べて，有意に（$p<0.05$）高いことからも裏付けられている．

おわりに

現在わが国の介護を受けている人々は 440 万人いるとされている．このうち，主な介護要因となっているものは男女とも脳血管障害と骨折・転倒であり，これらの２要因は寝たきりの原因としても介護要因同様１位と２位を占めるもので，両者と併せると 50% 以上にも相当するといわれている．この脳血管障害の基礎疾患は動脈硬化で，高血糖，

高脂血症，高血圧を放置し続けると，動脈硬化を呈し，やがて，脳血管障害である脳卒中をはじめ，心筋梗塞，さらには糖尿病の合併症である腎症や網膜症が悪化し，人工透析や失明に至るとされている．

また，この骨折とは骨粗鬆症性の骨折であり，骨粗鬆症も骨折を来たすと，途端にQOL・ADLの低下をもたらす．脳血管障害と骨粗鬆症は一見関係なさそうであるが，両者の疾患関連性は臨床的にも実証され，さらには細胞生物学的にも示唆されている．すなわち，骨代謝を営む破骨細胞の活性を元来は促進するRANKLは動脈硬化の進展にも，また破骨細胞活性を抑制するOPG(osteoprotegirin)は動脈硬化の防止にも作用するといわれている．このように骨粗鬆症による骨折と動脈硬化，ひいては心血管系イベントは個人に集積して出現することが判明しつつある．したがって更年期から取り組む骨格と血管系を守る意義は，女性のライフイベントを阻止する上で最も重要な課題となっており，そのヘルスケアのもつ意義は超高齢社会を迎え，さらに増大している．

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ORIGINAL ARTICLE

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Effect of physical activity and nutrition on bone mineral density in young Japanese women

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Abstract We explored factors that contributed to bone mineral density (BMD) in Japanese young women by quantifying the factors related to BMD. Between October 2003 and February 2004, we conducted a cross-sectional survey to study the status of nutritional intake and physical activity, and evaluated the various physical and serum parameters in relation to BMD. Subjects included 254 healthy female students who were 19–25 years old and were attending the Nursing School of Tokyo Women's Medical University, Japan. We measured the lumbar BMD (L2–L4) in these women. Multiple regression analysis was used to predict factors that contributed to current L2–L4 BMD. Our results showed that body mass index (BMI) (standardized regression coefficient = 0.45, $P < 0.0001$), past exercise habit (standardized regression coefficient = 0.15, $P < 0.0059$), and current total energy expenditure (standardized regression coefficient = 0.12, $P < 0.03$) were factors that significantly predicted the current L2–L4 BMD, with BMI as a key contributing factor. A BMI of $20.8\,kg/m^2$ allowed acquisition of young adult mean (YAM) irrespective of the total energy expenditure. In subjects with low BMI, L2–L4 BMD increased with higher current energy expenditure. A BMI of $20.8\,kg/m^2$ or greater and an energy expenditure of 32.9 METS-h/day or greater are required to acquire the YAM. We concluded that BMI and physical activity were factors that affected the BMD of Japanese young women.

Key words bone mineral density · osteoporosis · prevention · nutrition intake · physical activity

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Introduction

Osteoporosis is a disease associated with an increased risk for bone fractures as a result of a marked decrease in bone strength [1]. Bone strength is represented by a comprehensive measure of bone mineral density (BMD), bone quality, and bone structure [2]. In Japan, if patients with BMD suggestive of osteoporosis or osteopenia have fractures, the diagnosis of osteoporosis is deemed appropriate and pharmacological intervention is indicated [3]. Therapeutic intervention for osteoporosis is to prevent bone fractures. The incidence of bone fractures in the Japanese elderly population is estimated at 5%–10% annually, and this incidence increases with aging [4]. Osteoporosis has been increasing steadily worldwide in recent years. Femoral neck fractures are estimated to affect as many as 3 million people worldwide in 2025, compared with 1.3–1.7 million in 1900 [5].

Osteoporosis is among the diseases that may be amenable to treatment through lifestyle modification or management. This view has its premise from three research-confirmed hypotheses: (1) BMD increases over time until the age of 20 and remains stable until the age of 44; (2) early acquisition of high BMD helps prevent a steep drop in BMD in later years; and (3) appropriate exercise and nutritional intake are essential in the acquisition of BMD. For the Japanese population, a clear rationale for these hypotheses is yet to be established [6–8]. We designed a cross-sectional study to explore the factors that contribute to an increase of BMD among young women and to quantify each of the factors required for the acquisition of the reference BMD value. Exercise plays a crucial role in the prevention of osteoporosis and in the enhancement of bone mass. Non-Japanese epidemiological studies [9,10] showed that physical activities and sports during growing years affect bone mass status in the perimenopausal period, and calcium intake is an additive contributing factor. There is one published study that evaluated nutritional intake in premenopausal Japanese women [11] but it did not address the impact of exercise on bone mass. Another report evaluated the impact of both exercise and nutritional intake on bone mass in premenopausal young women [12], but the study involved only a small number of subjects and their results were inconsistent.

Subjects and methods

Between October 2003 and February 2004, we conducted a cross-sectional survey with 254 female students, aged 19–25, attending the Nursing School of Tokyo Women's Medical University, Tokyo, Japan. These students were healthy female volunteers who gave prior written informed consent. Subjects who had conditions that could affect bone mass or were receiving medications which could affect bone mass were excluded from the study. For all subjects under age 20, informed written consents were also obtained from their parents or guardians. Those who had prior treatment or who were receiving treatment that could affect bone metabolism, and those in pregnancy or in the lactation period, were also excluded from the study.

Information about age, birth weight, age at menarche, and current menstrual status was obtained. Height and body weight were measured, and the BMD of the lumbar vertebrae 2–4 (L2–L4) was also measured using a QDR 4500 DEXA bone densitometer (Hologic, Waltham, MA, USA). The Japanese young adult mean (YAM) of L2–L4 BMD defined by the QDR was $1.011 \pm 0.119\,g/cm^2$ [13]. For this study, L2–L4 BMD of $1.00\,g/cm^2$ was used as the reference mean. The manufacturer's lumbar spine phantom was scanned daily for quality control and to correct for instrument drift. Our observed coefficient of variation for the day-to-day quality control scans was <0.7%, which fell within the limit defined in the manufacturer's manual.

Laboratory serum evaluations included calcium, phosphorus (P), albumin (Alb), intact-osteocalcin (I-OC), cross-linked N-telopeptide of type I collagen (NTX), bone alkaline phophatase (BAP), osteoprotegerin (OPG), and soluble receptor activator of NF-κB ligand (sRANKL). The enzyme immunosorbent assay (EIA) method was used for i-OC, BAP, and NTX, and the enzyme-linked immunosorbent assay (ELISA) method for OPG and sRANKL.

Questionnaires were used to investigate energy intake and energy expenditures. The study protocol was approved by the Ethics Committee of Tokyo Women's Medical University.

Questionnaire used

Diet

Total energy expenditure and the intake of various nutrients such as calcium and vitamins were assessed using the self-administered 1-month recall Diet History Questionnaire (DHQ) developed by Sasaki et al. [14].

Physical activity

Information on past exercise (6–18 years of age) and current physical activity was assessed using the Japan Arteriosclerosis Longitudinal Study (JALS) Physical Activity Questionnaire (PAQ) [15]. The PAQ assesses current overall daily activity encompassing sleep, work, housework, exercise, and leisure. The questionnaire allows total energy and activity-specific energy to be quantified in terms of metabolic equivalent –hour/day (METs-h/day).

Statistical analysis

The subjects' demographic information, laboratory findings, nutritional intake, and physical activities were examined for correlation with L2–L4 BMD (Spearman's rank-correlation coefficient, $P < 0.05$). Factors that significantly correlated with the acquisition of L2–L4 BMD and factors that are generally thought to be associated with BMD were used as independent variables in a multiple regression analysis ($P < 0.01$). Continuous variables that were found to be significant in the multiple regression analysis were determined by analysis of variance (ANOVA, $P < 0.05$).

Results

A total of 254 subjects were enrolled in the study. The demographic profile of the subjects is given in Table 1. The mean BMD of the L2–L4 was $1.00\,g/cm^2$. A total of 53 subjects (20.9%) had abnormal menstruation, but the BMD of L2–L4 in the subjects who had irregular menstruation and in those who had regular menstruation were not different.

Table 1. Demographic characteristics of study subjects ($n = 254$)

Variables	Unit	Mean SD
Age	Years	20.7 ± 1.5
Weight at birth*a	g	3146.1 ± 438.8
Age at menarche	Years	11.9 ± 1.2
Height	cm	158.5 ± 4.9
Body weight	kg	53.5 ± 7.8
Body mass index	kg/m^2	21.3 ± 2.8
Lumbar vertebrae 2–4 BMD	g/cm^2	1.00 ± 0.11
Ca	mg/ml	9.5 ± 0.3
P	mg/dl	3.7 ± 0.4
ALB	g/dl	4.9 ± 0.2
I-OC	ng/ml	8.4 ± 2.8
NTX	nMBCE/l	13.5 ± 4.5
BAP	U/l	22.3 ± 6.5
OPG*b	pmol/l	3.62 ± 2.24
sRANKL*c	pmol/l	0.33 ± 0.27

*a,*b,*c Sample size was different from the total: *a = 242, *b = 250, *c = 242

BMD, bone mineral density; Ca, serum calcium; P, serum phosphorus; ALB serum albumin; I-OC, serum intact osteocalcin; NTX, serum crosslinked N-telopeptide of type I collagen; BAP, serum alkaline phosphatase (bone type isozyme); OPG, serum osteoprotegerin; sRANKL, serum-soluble receptor activator of NF-κB ligand

Table 2. Daily nutritional intake and physical activity ($n = 254$)

Variables	Unit	Mean SD
Nutritional intake as assessed by DHQ		
Proteins	g/day	50.1 ± 18.3
Lipids	g/day	56.9 ± 20.5
Carbohydrates	g/day	237.8 ± 54.8
Fatty acids	g/day	47.8 ± 17.7
Calcium	mg/day	497.8 ± 224.8
Phosphorus	mg/day	914.3 ± 316.6
Magnesium	mg/day	129.9 ± 30.2
Alcohol	g/day	5.0 ± 9.4
Cholesterol	mg/day	260.9 ± 115.4
Vitamin D	µg/day	11.6 ± 7.3
Vitamin K	µg/day	259.7 ± 161.1
Retinol	µg/day	244.0 ± 176.8
Current physical activity		
Total energy expenditure	METs-h/day	33.4 ± 2.6
Energy expenditure for exercise	kcal/day	221.0 ± 75.1

DHQ, Diet History Questionnaire; PAQ, Japan Arteriosclerosis Longitudinal Study (JALS) Physical Activity Questionnaire

None of the subjects experienced long hospitalization or skeletal diseases in childhood.

Nutritional intake and physical activity

The daily nutritional intake (mean ± SD) for each nutrient and PAQ results are shown in Table 2. A total of 20 (7.9%) subjects reported that they regularly exercised in the past.

Factors correlated with L2–L4 BMD

Factors found to correlate with the L2–L4 BMD are shown in Table 3: height, body weight, body mass index (BMI), birth weight, BAP, I-OC values, cholesterol intake as calculated based on the DHQ, and current total energy expenditure as calculated based on the PAQ, significantly correlated with the L2–L4 BMD.

Multiple regression analysis

All factors that significantly correlated with L2–L4 BMD (BMI, birth weight, i-OC, BAP, cholesterol, past exercise, and total energy expenditure) and factors that are generally thought to affect BMD (intake of calcium, vitamin D, vitamin K, phosphorus, and magnesium) were used as independent factors, and current L2–L4 BMD was used as a dependent variable in the multiple regression analysis (Table 4). The results showed that BMI, past exercise, and current total energy expenditure significantly contributed to the current L2–L4 BMD, with BMI being the key contributing factor.

L2-L4 BMD values by BMI and total energy expenditure level

To quantify the factors required for the acquisition of the reference L2–L4 BMD, the subjects were divided into four

Table 3. Correlation between lumbar vertebral 2–4 BMD, background parameter, serum parameter, nutrition intake, and physical activity

Item	Correlation coefficient	*P* value
Demographic parameters		
Age	0.008	0.895
Height	0.18	0.004
Body weight	0.479	<0.0001
BMI	0.444	<0.0001
Age at menarche	–0.122	0.053
Weight at birth	0.181	0.005
Serum parameters		
Ca	–0.041	0.52
P	–0.064	0.309
I-OC	–0.294	<0.0001
NTX	–0.06	0.338
BAP	–0.132	0.036
ALB	–0.02	0.757
OPG	0.006	0.932
sRANKL	0.101	0.117
Nutritional intake (DHQ)		
Proteins	0.065	0.3
Lipids	0.022	0.723
Carbohydrates	–0.044	0.481
Fatty acids	0.007	0.916
Calcium	0.061	0.333
Phosphorus	0.095	0.133
Alcohol	0.013	0.842
Cholesterol	0.172	0.006
Vitamin D	0.059	0.348
Vitamin K	0.061	0.332
Retinol	0.054	0.39
Current physical activity		
PAQ		
Past exercise	0.077	0.003
Total energy expenditure	0.184	0.003
Hours of exercise	0.034	0.587
Accelerometer		
Total energy expenditure	–0.3	<0.0001
Number of steps taken	0.021	0.74

BMD, bone mineral density; Ca, serum calcium; P, serum phosphorus; ALB, serum albumin; I-OC, serum intact osteocalcin; NTX, serum crosslinked N-telopeptide of type I collagen; BAP, serum alkaline phosphatase (bone type isozyme); DHQ, Diet History Questionnaire; PAQ, Physical Activity Questionnaire by Japan Arteriosclerosis Longitudinal Study

Table 4. Factors found to predict the current lumbar vertebral 2–4 BMD with a significance level of $P < 0.01$ by multiple regression analysis

Variable	Regression coefficient	P value	Standardized regression coefficient
BMI	0.01813	<0.0001	0.45201
PAQ exercise in past	0.06236	0.0059	0.15034
PAQ total energy expenditure	0.005	0.0329	0.11667

PAQ, Japan Arteriosclerosis Longitudinal Study (JALS) physical activity questionnaire

Table 5. Analysis of lumbar vertebral 2–4 BMD (g/cm^2) in subjects divided into four groups by median BMI and current total energy expenditure

	BMI (kg/m^2)	
	<20.8	≧20.8
Current total energy expenditure (METs/day)		
<32.9	0.94 ± 0.10	1.04 ± 0.12
≧32.9	0.98 ± 0.10	1.04 ± 0.10

Data shown as mean ± SD
METs, metabolic equivalent; BMI, body mass index
ANOVA, $P < 0.001$

groups by median BMI and energy expenditure (Table 5). As a result, the subjects with higher BMI (≥20.8 kg/m^2) were associated with the highest L2–L4 BMD, while those with lower BMI (<20.8 kg/m^2) and total energy expenditure (<32.9 METs-h/day) were associated with the lowest L2–L4 BMD. This analysis showed that the subjects with higher BMI (≥20.8 kg/m^2) showed more than 1.04 g/cm^2, mean values of L2–L4 BMD, regardless of their current total energy expenditure.

Discussion

Babarousti et al. [16] reported that BMI, Ca intake, and time spent on physical activity affect heel BMD independently but not in an age-dependent manner. However, our cross-sectional survey is the first study to clearly demonstrate that L2–L4 BMD was positively correlated with BMI, past exercise, and current total energy expenditure after adjusting for other confounding factors.

BMI and current total energy expenditure are manageable lifestyle factors. Therefore, lifestyle management that addresses and corrects these factors in a timely fashion may prevent osteoporosis among Japanese women. Our study showed that young Japanese women with a BMI >20.8 kg/m^2 met the reference mean L2–L4 BMD or had the potential to acquire the reference mean with sufficient exercise. Slimness is considered a risk factor for osteoporosis. In our study, the lowest quartile of BMI (20.8 kg/m^2) fell within the normal range of the WHO criteria, which define slimness as BMI 18.5 kg/m^2 or less. However, our study showed that the BMD of the subjects who had a BMI of 20.8 kg/m^2 or more was higher than the Japanese YAM.

A total energy expenditure of 32.9 METs-h/day translates into 1650 kcal/day in a person weighing 50 kg with an oxygen intake of 1 kcal/kg/h in a resting, sitting position; this comes very close to the assumed total energy expenditure of 1550 kcal/day among women of the same age group with low-intensity physical activity [17]. Thus, the mean total energy expenditure of 33.4 METs-h/day measured in our subjects indicates that young women with this level of physical activity met the Japanese YAM. In other words, without recourse to extra physical activity, these women will likely achieve an L2–L4 BMD of 1.00 kg/cm^2 by maintaining just the total energy expenditure level required for daily living.

Past exercise also significantly correlated with L2–L4 BMD in our female subjects. In young women, physical activity generating a high impact is assumed to contribute toward increasing BMD of the femoral neck and other sites of bone that are susceptible to weight loading. Physical activity of a low to moderate intensity is thought to indirectly increase areal BMD by building muscle strength [17]. A report shows that a 10-month high-impact exercise among premenarcheal girls resulted in an increase in both muscle strength and BMD [18]. Furthermore, an 8-month moderate-intensity exercise intervention among prepubertal boys resulted in an increase of areal BMD [19]. These studies suggest that bone is highly responsive to exercise intervention in early years; additionally, it is also assumed that the effect of this exercise may persist well into adulthood [20]. Thus, exercise in growing years appears to play a pivotal role in preventing osteoporosis in later years. Our study confirmed these observations by clearly showing that past physical activity correlated with high L2–L4 BMD. Generally, it also appears that the impact of exercise on L2–L4 BMD is greatest during the few years immediately following menarche when the rate of increase in BMD becomes the highest. Our data on past physical activity may yield additional insights into establishing an exercise methodology required for acquisition of high L2–L4 BMD. Further analysis on the kinds, intensities, durations, and frequencies of the physical activities reported in our study is currently under way.

Only a few reports suggested a potential synergy between calcium intake and exercise [21]. Results with regard to the relationship between calcium intake and peak bone mass were disparate. Greater calcium intake is thought to contribute to the acquisition of a high peak bone mass. A meta-analysis showed that calcium intake correlated with BMD of all areas except in the ulna of postmenopausal women

[22]. Another meta-analysis by Cumming et al. [23] indicated that calcium intake has no appreciable role in preventing fractures. This finding was in agreement with still another meta-analysis published recently [24] that showed no clear correlation between dietary calcium intake and femoral neck fractures. Thus, the relationship between calcium intake and fractures remains far more elusive than that between calcium intake and BMD. Our study did not support the view that calcium intake influences BMD. In addition, the intake of other nutrients did not yield much insight into other factors that would affect BMD values.

The limitation of this study was its cross-sectional design, which could sometimes be misleading in presenting a true causal relation. A longitudinally designed study is needed to confirm the finding obtained in this study.

In summary, our study showed that BMI, past exercise, and physical activity are factors that correlate with current L2–L4 BMD among Japanese young women. A BMI of 20.8 kg/m^2 allowed the acquisition of the Japanese young adult reference mean (YAM) L2–L4 BMD of 1.00 g/cm^2, irrespective of the physical activity. The subjects with a BMI of 20.8 kg/m^2 or greater and a physical activity of 32.9 METS-h/day or greater had the YAM BMD. We concluded that BMI and physical activity were factors that affected the BMD of Japanese young women. BMI is more likely to impact on BMD than physical activity.

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