bone strength, a composite endpoint combining both bone quality and density, diminishes considerably. In clinical studies, an accurate evaluation of bone density and quality is carried out by using the dual-energy X-ray absorptiometry (DXA) method and by the use of appropriate bone metabolism makers.

A negative correlation between vascular sclerosis and BMD has already been reported [5–8]. However, DXA has seldom been used for evaluation of bone density, and studies exploring the association between vascular sclerosis and bone metabolism markers are very few.

This study aimed to elucidate the relationship between arteriosclerosis and osteoporosis in postmenopausal women by examining their baPWV, bone mineral density by using DXA, and bone metabolic markers for association among these variables.

Subjects and methods

Subjects

This study enrolled 143 postmenopausal women who visited the Menopause Clinic in our department from January 2004 to April 2005. Their menopausal status was confirmed by interview, where those who had not menstruated for 12 months were considered to be menopausal. Those who could not precisely recall the date of their last menstrual period or who did not answer the questionnaire were excluded from the study. None of the subjects had undergone hormonal replacement therapy or had taken any steroid hormones. Women who had hypertension, diabetes, dyslipidemia or osteoporosis took appropriate medication for the condition (Table 1).

Informed consent was obtained from every subject who enrolled in the study. The study protocol was then approved by the Ethics Committee of Tokyo Women's Medical University.

Measurement of pulse wave velocity

All subjects underwent brachial-ankle pulse wave velocity (baPWV) measurement as an index for arteriosclerosis, using a form pulse wave velocity/ankle brachial pressure index (form PWV/ABI) (Nippon Coli). Details of the methodology have been described previously [8].

The subjects were examined while resting in a supine position with the measurement device set to simultaneously record PWV, blood pressure, electrocardiogram and heart sounds. Electrocardiogram electrodes were placed on both wrists, and a heart sound microphone was placed over the left sternal border. The cuffs were wrapped around both arms and ankles and connected to the plethysmographic sensors to evaluate brachial and post-tibial arterial pressure waveforms and volume pulse forms in the subjects. The subjects were also connected to oscillometric sensors to measure blood pressure. baPWV was measured in all subjects after they had rested for at least 5 min. The mean left and the right baPWV values for each subject were used for analysis.

Table 1 Clinical characteristics of 143 women in this study

Age (years)	57.9 ± 8.3
Height (cm)	155.7 ± 5.2
Weight (kg)	55.3 ± 9.4
BMI (kg/m^2)	23.0 ± 3.6
sBP (mmHg)	128.3 ± 21.6
dBP (mmHg)	76.1 ± 12.2
iPTH (pg/ml)	48.3 ± 19.9
Ca (mg/dl)	9.2 ± 0.8
Urinary Ca/Cr	0.18 ± 0.39
P (mg/dl)	3.6 ± 0.4
NTx (nmolBCE/mmol Cr)	43.1 ± 20.0
BMD (g/m^2)	0.884 ± 0.154
PWV (cm/s)	1,450 ± 261
BAP (IU/l)	25.0 ± 11.2
No. of subjects with	
Hypertension	3
Diabetes mellitus	5
Dyslipidemia	44
Osteoporosis	25
Age at menopause (years)	48.0 ± 5.0

All results are presented as the mean ± SD

BMI body mass index, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *iPTH* intact parathyroid hormone, *NTx* urine cross-linked *N*-telopeptides of type 1 collagen, *BAP* bone alkaline phosphatase

Measurement of bone mineral density

Lumbar spine (L2–L4) BMD was measured by using DXA (QDR4500, Hologic Inc., USA) as an index for osteoporosis. BMD values were reported as grams per square centimeter.

Laboratory measurements

The following variables were evaluated: blood Ca, P and intact PTH levels; urine Ca/Cr ratios; bone alkaline phosphatase (BAP) levels; and urine cross-linked telopeptides of type I collagen (NTx).

Statistical analysis

Data were expressed as mean ± SD. Simple regression analysis was used to examine correlation between baPWV,

BMD and other clinical variables. Multiple regression analysis was further performed for baPWV, BMD and other clinical variables. A value of $P < 0.05$ was considered statistically significant.

Results

Table 1 summarizes the characteristics of the subjects. There was a significant negative correlation between PWV and BMD in the 143 patients studied ($r = -0.21$; $P = 0.0135$) (Table 2). When each of the parameters evaluated was examined for possible correlation with PWV and BMD, there was a positive correlation between PWV and blood pressure, with a stronger correlation found between PWV and systolic blood pressure ($r = 0.734$; $P < 0.0001$). A positive correlation was also present between PWV and bone ALP (BAP) ($r = 0.166$; $P = 0.047$) (Table 2). BMD showed a positive correlation with both body weight and BMI, where a stronger correlation was seen between BMD and body weight ($r = 0.506$; $P < 0.0001$) (Table 2). Given these results, patients with hypertension (defined as sBP 140 mmHg or higher or dBP 90 mmHg or higher), a factor affecting PWV values, and those with BMI less than 18.5 as well as those with BMI more than 25, a factor affecting BMD, were all excluded from the study. The remaining 75 subjects were subjected to further review. Analysis of these 75 subjects showed a more significant negative correlation between PWV and BMD

Table 2 Univariate analysis of clinical factors correlated with brachial-ankle pulse wave velocity (baPWV) and lumbar bone mineral density (BMD)

	With baPWV		With BMD	
	r	*P*	*r*	*P*
Age	0.587	<0.0001	0.283	0.0006
Height	0.311	0.0002	0.191	0.169
Weight	0.006	NS	0.506	<0.0001
BMI	0.128	NS	0.453	<0.0001
sBP	0.734	<0.0001	0.026	NS
dBP	0.564	<0.0001	0.074	NS
BMD/baPWV	0.206	0.0135	0.206	0.0135
Ca	0.072	NS	0.090	NS
P	0.148	0.0793	0.026	NS
Urinary Ca/Cr	0.044	NS	0.028	NS
iPTH	0.140	0.0947	0.017	NS
NTx	0.030	NS	0.051	NS
BAP	0.166	0.0470	0.018	NS

BMI body mass index, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *iPTH* intact parathyroid hormone, *NTx* urine cross-linked *N*-telopeptides of type 1 collagen, *BAP* bone alkaline phosphatase

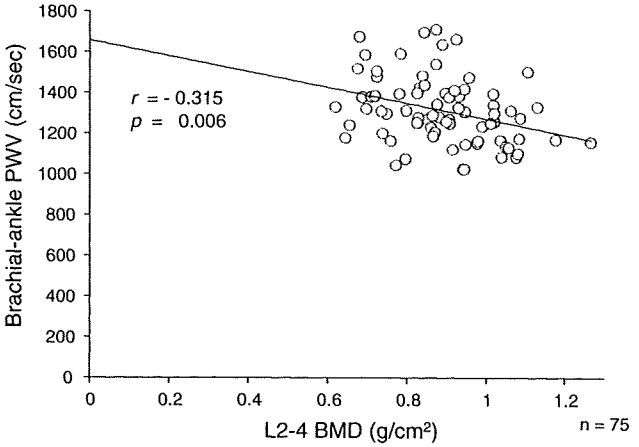

Fig. 1 An even stronger correlation was observed between L2–L4 BMD and PWV values after those with hypertension, a determining factor of PWV, and those with obesity as assessed by BMI, a determining factor of L2–L4 BMD, were excluded ($r = -0.315$; $P = 0.006$)

($r = -0.315$; $P = 0.006$) than in the earlier analysis from which no subjects were excluded (Fig. 1).

In order to eliminate the possibility of age affecting the results, the subjects were age-matched and then stratified into three groups by bone density, i.e., normal BMD ($n = 17$, L2–L4 BMD, 0.962 ± 0.085 g/cm^2), osteopenic ($n = 12$, 0.755 ± 0.029) and osteoporotic ($n = 9$, 0.673 ± 0.028). No significant difference was observed among these three groups concerning their age and blood pressure (Table 3). The subjects with normal BMD showed significantly lower PWV values than the other two groups (Fig. 2). Hence, a significant correlation between PWV and BMD was confirmed to be present even after adjustment for age among the subjects.

In the remaining 75 patients, PWV values showed a stronger positive correlation with the bone metabolism marker BAP ($r = 0.248$; $P = 0.032$) than when all subjects were included for analysis ($r = 0.166$; $P = 0.047$) (Fig. 3). Comparison of PWV values among the BAP tertiles showed that the tertile with the highest BAP showed significantly higher PWV values than the other tertiles ($P < 0.05$) (Fig. 4). A further examination by multiple regression analysis showed no correlation between PWV and BMD or between PWV and BAP (Table 4).

Discussion

Our study results demonstrate that PWV and BMD are negatively correlated in postmenopausal women. In addition, the greater the PWV values, and the more sclerotic the blood vessels are, the lower the lumbar L2–L4 BMD values. Of note, this negative correlation was shown to be particularly pronounced among women with normal

Table 3 Background factors in the three groups aged-matched and stratified by BMD

	Osteoporotic	Osteopenic	Normal BMD	*P*
Number	9	12	17	
BMD (g/m^2)	0.067 ± 0.028	0.755 ± 0.029	0.962 ± 0.085	<0.05
Age (years)	57.8 ± 8.1	57.6 ± 8.1	57.3 ± 5.2	NS
Height (cm)	155.0 ± 4.3	153.3 ± 4.4	157.2 ± 6.3	NS
Weight (kg)	49.6 ± 4.0	49.0 ± 5.1	54.9 ± 6.8	<0.05
BMI (kg/m^2)	20.6 ± 0.9	21.1 ± 1.8	22.1 ± 1.7	<0.05
sBP (mmHg)	120 ± 11	114 ± 13	11 ± 10	NS
dBP (mmHg)	71 ± 9	71 ± 8	66 ± 10	NS
iPTH (pg/ml)	47.2 ± 13.5	40.6 ± 11.9	46.8 ± 16.7	NS
Ca (mg/dl)	9.3 ± 0.3	9.3 ± 0.3	9.4 ± 0.6	NS
Urinary Ca/Cr	0.13 ± 0.08	0.16 ± 0.12	0.14 ± 0.07	NS
P (mg/dl)	3.5 ± 0.3	3.7 ± 0.2	3.6 ± 0.3	NS
NTx (nmolBCE/mmol Cr)	42.0 ± 22.5	48.2 ± 26.8	43.6 ± 21.1	NS
BAP (IU/l)	25.9 ± 8.1	24.6 ± 7.5	20.4 ± 6.5	NS

BMI body mass index, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *iPTH* intact parathyroid hormone, *NTx* urine cross-linked *N*-telopeptides of type 1 collagen, *BAP* bone alkaline phosphatase

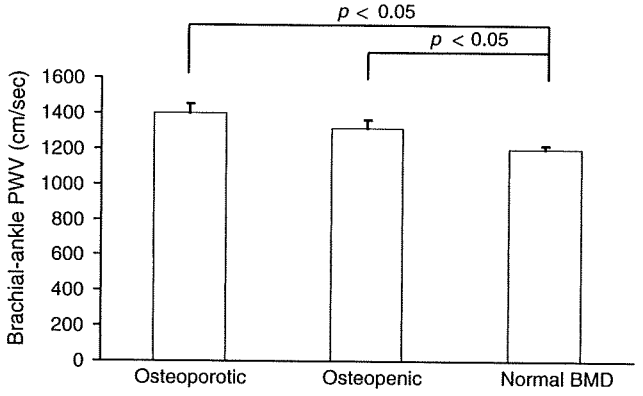

Fig. 2 The subjects in the normal BMD group showed significantly lower PWV values than the other two groups (1,201.1 ± 18.3 vs. 1,312.6 ± 49.0 cm/s, 1,201.1 ± 18.3 vs. 1,399.5 ± 54.1 cm/s; $P < 0.05$). All results are presented as mean ± SD. In these subjects, a significant negative correlation was shown between PWV and BMD even after they were adjusted for age

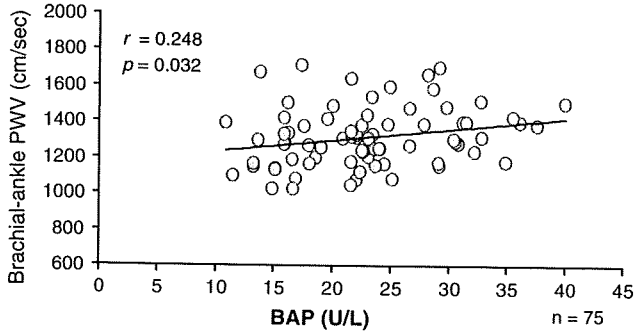

Fig. 3 PWV values showed a stronger positive correlation with BAP, a bone formation marker, in 75 subjects with normal blood pressure and BMI ($r = 0.248$; $P = 0.032$)

physique and blood pressure. Furthermore, this correlation was confirmed even when the data were adjusted for age, suggesting that decreased bone mass is a risk factor for atherosclerosis, independently of other risk factors, such as hypertension, diabetes or smoking. Our results are in agreement with the report of Hirose et al. [7] that demonstrated correlation between increased PWV and reduced calcaneal quantitative osteo-sono index as assessed by quantitative ultrasound (QUS). In recent years, similar findings have been reported not only in cross-sectional, but also in longitudinal studies [6, 11] that were conducted across races. These studies began to clarify the cellular mechanisms of pathogenesis implicated in both atherosclerosis and decreased bone mass [12, 13]. An osteoblast- or chondrocyte-like phenotypic transformation of vascular smooth muscle cells and myofibroblasts is assumed to be implicated in the process of vascular calcification, suggesting a role for osteochondral metabolism-associated factors in this process [14–16]. While aging and menopause are clinical risk factors for both atherosclerosis and osteoporosis, other factors, such as various inflammatory processes, oxidative stress and homocystein, are also reported as risk factors for both conditions [17].

The interrelationship between atherosclerosis and bone metabolism has been corroborated by the fact that anti-atherosclerotic and anti-resorptive agents exert effects on bone metabolism and on atherosclerosis [18, 19]. In this regard, statins as therapeutic agents for hypercholesterolemia are known to exert their anti-atherosclerotic effects through inhibition of HMG-CoA reductase, a key enzyme in the rate-limiting step of the mevalonate pathway; they have also been shown to mediate BMP-2 promoter activation. In both mouse calvarial cultures and in clinical trials [20, 21], statins were shown to increase the number of osteoblasts as well as new bone mass, suggesting a potential role for statins as a new class of pro-osteogenic

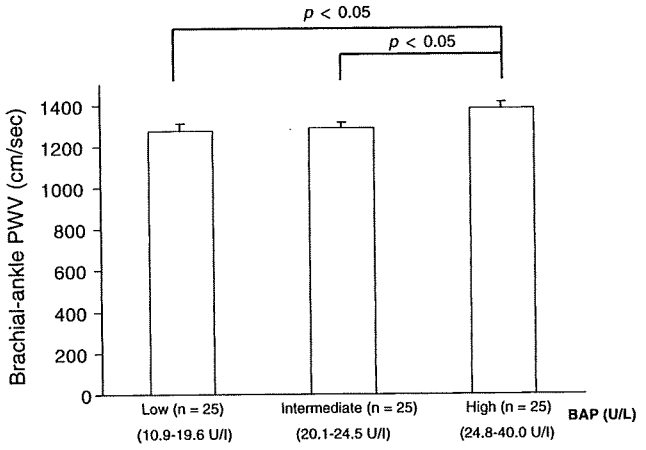

Fig. 4 The tertile with the highest BAP showed significantly higher PWV values than the other tertiles (1,308.8 ± 35.0 vs. 1,285.5 ± 27.6 cm/s, 1,308.8 ± 35.0 vs. 1,247.9 ± 35.6 cm/s; $P < 0.05$)

Table 4 Correlation of PWV and other factors as assessed by multiple regression analysis with a significance level of $P < 0.05$

Variable	Regression coefficient	*P* value	Standardized regression coefficient
Age	11.42	<0.001	262.58
Height	−3.72	0.115	−52.11
sBP	6.98	<0.001	408.06
BMD	−99.78	0.213	−35.27
BAP	1.89	0.171	42.06

sBP systolic blood pressure, *BAP* bone alkaline phosphatase

agents. On the other hand, bisphosphonates as anti-osteoporotic agents have been shown to suppress osteoclast activation as part of their mechanism of action that inhibits the mevalonate pathway [22]. Thus, together, these results suggest that statins and bisphosphonates may act on, and exert similar effects on, the same cells.

In our present study as well, BAP and PWV were found to be correlated, consistently with previous reports showing that when osteoporotic patients were stratified by presence or absence of aortic calcification, those with aortic calcification were associated with significantly higher BAP values [23]. It is also reported that BAP was significantly expressed in calcified vascular smooth muscle cells. Furthermore, in the presence of pro-inflammatory cytokines, there is an increase in the BAP level, thus further promoting vascular calcification [24]. These findings appear to point towards the possibility that BAP values reflect the degree of arteriosclerosis present and that osteoblast-like cells are implicated in arteriosclerosis.

In our analyses using multiple linear regression, we were unable to establish a clear relationship between PWV and BMD or between PWV and BAP. However, the results obtained from the stratified groups do not necessarily exclude the possibility of such relationship, as shown in a comparison of PWV values among the BAP tertiles. The main limitation of this study lies in the fact that the study subjects were not adequately uniform; the study subjects varied greatly in age and included those with medical conditions such as hypertension and diabetes. The limited availability of appropriate cases further enhanced the study limitation. Therefore, increasing the number of subjects, which also helps to ensure inclusion of uniform subjects, may contribute towards a better clarification of the relationship between bone and vasculature.

The management of bone metabolic disorders needs to focus not only on the disease per se, but also on the resulting vascular calcification that will likely lead to ectopic calcification, thus affecting the overall prognosis of affected patients. Mounting evidence suggests a strong correlation between vascular calcification and bone mineral content. While the implication of this finding remains to be further explored, current evidence appears to suggest a role for BMD measurement as an important index that assists in the management of vascular calcification.

It is suggested that patients with low bone mass should undergo careful monitoring for atherosclerosis to better manage the condition, where therapeutic intervention may also be considered. In a fast-aging society, such an approach is not only needed for the health of people and for the social care workers caring for them, but also for health economic reasons.

References

1. Mendelsohn ME, Karas RH (1999) The protective effects of estrogen on the cardiovascular system. N Engl J Med 340:1801–1811
2. Mosca L (2000) The role of hormone replacement therapy in the prevention of postmenopausal heart disease. Arch Intern Med 160:2263–2272
3. 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
4. Soda MY, Mizunuma H, Honjo S, Okano H, Ibuki Y, Igarashi M (1993) Pre- and postmenopausal bone mineral density of the spine and proximal femur in Japanese women assessed by dual-energy x-ray absorptiometry: a cross-sectional study. J Bone Miner Res 8:183–189
5. Barengolts EI, Berman M, Kukreja SC, Kouznetsova T, Lin C, Chomka EV (1998) Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. Calcif Tissue Int 62:209–213
6. Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC (2000) Progression of aortic calcification is associated with

metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol 20:1926–1931
7. Hirose K, Tomiyama H, Okazaki R, Arai T, Koji Y, Zaydun G, Hori S, Yamashina A (2003) Increased pulse wave velocity associated with reduced calcaneal quantitative osteo-sono index: possible relationship between atherosclerosis and osteopenia. J Clin Endocrinol Metab 88:2573–2578
8. Jorgensen L, Joakimsen O, Rosvold Berntsen GK, Heuch I, Jacobsen BK (2004) Low bone mineral density is related to echogenic carotid artery plaques: a population-based study. Am J Epidemiol 160:549–556
9. Munakata M, Ito N, Nunokawa T, Yoshinaga K (2003) Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am J Hypertens 16:653–657
10. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y (2002) Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 25:359–364
11. Kado DM, Browner WS, Blackwell T, Gore R, Cummings SR (2000) Rate of bone loss is associated with mortality in older women: a prospective study. J Bone Miner Res 15:1974–1980
12. Collin-Osdoby P (2004) Regulation of vascular calcification by osteoclast regulatory factors RANKL and osteoprotegerin. Circ Res 95:1046–1057
13. Hofbauer LC, Schoppet M (2004) Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 292:490–495
14. Abedin M, Tintut Y, Demer LL (2004) Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol 24:1161–1170
15. Dhore CR, Cleutjens JP, Lutgens E, Cleutjens KB, Geusens PP, Kitslaar PJ, Tordoir JH, Spronk HM, Vermeer C, Daemen MJ (2001) Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 21:1988–2003
16. Vattikuti R, Towler DA (2004) Osteogenic regulation of vascular calcification: an early perspective. Am J Physiol Endocrinol Metab 286:E686–E696
17. McFarlane SI, Muniyappa R, Shin JJ, Bahtiyar G, Sowers JR (2004) Osteoporosis and cardiovascular disease: brittle bones and boned arteries, is there a link? Endocrine 23:1–10
18. Bauer DC (2003) HMG CoA reductase inhibitors and the skeleton: a comprehensive review. Osteoporos Int 14:273–282
19. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G (1999) Stimulation of bone formation in vitro and in rodents by statins. Science 286:1946–1949
20. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyörälä K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L (1996) Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 156:2085–2092
21. Reid IR, Hague W, Emberson J, Baker J, Tonkin A, Hunt D, MacMahon S, Sharpe N (2001) Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term Intervention with Pravastatin in Ischaemic Disease. Lancet 357:509–512
22. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA (1999) Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. Proc Natl Acad Sci USA 96:133–138
23. Iba K, Takada J, Yamashita T (2004) The serum level of bone-specific alkaline phosphatase activity is associated with aortic calcification in osteoporosis patients. J Bone Miner Metab 22:594–596
24. Shioi A, Katagi M, Okuno Y, Mori K, Jono S, Koyama H, Nishizawa Y (2002) Induction of bone-type alkaline phosphatase in human vascular smooth muscle cells: roles of tumor necrosis factor-alpha and oncostatin M derived from macrophages. Circ Res 9:9–16

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Possible risk factor for postmenopausal women: Postprandial hypertriglyceridemia

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Abstract

Aim: To explore the clinical implications of postprandial hypertriglyceridemia in postmenopausal Japanese women.

Methods: Postprandial blood samples were collected from 91 women at their initial visit, with fasting blood samples collected within the following month to examine their lipid profiles. These women were grouped into normotriglyceridemia (fasting/postprandial triglycerides [TG] < 150; $n = 36$), mild postprandial hypertriglyceridemia (fasting TG < 150, postprandial TG ≥ 150, <225; $n = 27$), moderate postprandial hypertriglyceridemia (fasting TG < 150, postprandial TG ≥ 225; $n = 19$) and hypertriglyceridemia (fasting TG ≥ 150; $n = 9$) by using 225 mg/dL as the cut-off value for postprandial hypertriglyceridemia.

Results: The subjects were 54.1 ± 7.8 years old; their duration of menopause, 6.0 ± 7.7 years; body mass index, 21.4 ± 4.0 kg/m^2; postprandial TG concentration, 189 ± 110 mg/dL; and fasting TG concentration, 109 ± 50 mg/dL. Approximately 50% ($n = 46$) of the women had normal fasting TG (fasting TG < 150), but high postprandial TG (postprandial TG ≥ 150). Approximately 10% ($n = 9$) of the women had hypertriglyceridemia (fasting TG ≥ 150 mg/dL). In those with postprandial hypertriglyceridemia ($n = 46$), postprandial TG negatively correlated with high-density lipoprotein cholesterol (HDL-C), while fasting TG showed no such correlation with HDL-C.

Conclusion: Postprandial TG may provide a better understanding of lipid metabolism in postmenopausal women.

Key words: coronary heart disease, hormone replacement therapy, hypertriglyceridemia, postmenopause, postprandial hypertriglyceridemia.

Introduction

A decrease in the circulating estrogen concentration after menopause causes abnormalities in lipid metabolism leading to an increase in the incidence of ischemic heart disease in postmenopausal women. The results of the Women's Health Initiative, a large-scale randomized control trial,[1] demonstrated in 2002 that female patients receiving hormone replacement therapy (HRT) were associated with a hazard ratio of 1.24 for coronary artery disease, indicating that estrogen does not confer cardiac protection.

Although estrogen decreases low-density lipoprotein cholesterol (LDL-C) and increases high-density lipoprotein cholesterol (HDL-C),[2–5] it also carries the risk of ischemic heart disease and stroke partly because of an associated increase in triglycerides (TG).[6] Hypertriglyceridemia may decrease the size of LDL particles and contribute to an increase in insulin resistance.[7] All of these factors may therefore lead to the development of arteriosclerotic lesions.

Postprandial hypertriglyceridemia is also considered an independent predictor of ischemic heart disease.[8] We therefore compared fasting and postprandial

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blood samples to investigate the clinical implications of postprandial hypertriglyceridemia in postmenopausal Japanese women.

Methods

The subjects comprised 91 women who participated in an outpatient health maintenance program for middle-aged and elderly women implemented at our department between November 2000 and March 2003. Postprandial blood samples (taken after lunch) were collected from the subjects after lunch at their initial visit, with their fasting blood samples taken after 12 h of fasting during the following month. Normotriglyceridemia was defined as fasting TG < 150 mg/dL and the subjects were subgrouped into the following four groups by using 225 mg/dL as the cut-off value for postprandial hypertriglyceridemia: normotriglyceridemia ($n = 36$), mild postprandial hypertriglyceridemia ($n = 27$), moderate postprandial hypertriglyceridemia ($n = 19$) and hypertriglyceridemia ($n = 9$).

Statistical analyses were performed using Microexcel 2002. The Mann–Whitney *U*-test was used to compare the fasting lipid profiles of the four groups as stratified by TG concentration. A paired *t*-test was used to compare postprandial normotriglyceridemia and postprandial hypertriglyceridemia for lipid metabolism. ANOVA was used to test for differences in HDL-C between postprandial and fasting TG concentration. For all analyses performed, a *P*-value of 0.01 was considered statistically significant.

Results

Baseline characteristics of subjects

The mean age of the 91 women was 54.1 ± 7.8 years. Their physical findings were as follows: height, 156.5 ± 5.1 cm; body weight, 53.8 ± 7 kg; and body mass index, 21.4 ± 4 kg/m^2. Their duration of menopause was 6 ± 7.7 years.

Breakdown of results by TG concentration

The mean postprandial TG concentration was 187 ± 111 mg/dL, and the mean fasting TG concentration was 108 ± 50 mg/dL, with the mean difference (postprandial–fasting) being 85 ± 81 mg/dL. The postprandial TG concentration, compared with the fasting TG concentration, increased in 78 women (86%), did not change in one woman (1%) and decreased in 12 women (13%).

Table 1 Baseline characteristics of the women including their fasting and postprandial triglyceride (TG) concentrations ($n = 91$)

	n	%	Mean ± SD
Age (years)			54.1 ± 7.8
BMI (kg/m^2)			21.4 ± 4.0
<25	83	91.2	
≥25	8	8.8	
TC (mg/dL)			226.9 ± 34.0
LDL-C (mg/dL)			140.1 ± 32.5
HDL-C (mg/dL)			62.0 ± 15.7
Fasting TG (mg/dL)			108.9 ± 50.4
<150	82	90.9	
≥150	9	9.1	
Postprandial TG (mg/dL) (Fasting TG < 150)			187.0 ± 111.4
<150	36	40.0	
≥150, <225	27	30.0	
≥225	19	20.9	

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Relationship between postprandial TG and fasting TG concentrations (Table 1)

The TG concentration was normal (<150 mg/dL) in the fasting state but high in the postprandial state in 46 women, who accounted for approximately 50% of the women. True hypertriglyceridemia with a fasting TG concentration of ≥150 mg/dL was seen in nine women, comprising approximately 10% of all women. The postprandial TG concentrations in all of these women with hypertriglyceridemia were high (≥150 mg/dL).

Fasting serum lipid profile by TG classification

We found that HDL-C and TC were lower in those with postprandial hypertriglyceridemia than in those with normal TG ($P < 0.01$) (Table 2). Among the 46 women with postprandial hypertriglceridemia, we found a significant negative correlation between postprandial TG and HDL-C ($r = -0.43$, $P = 0.0081$) (Fig. 2). Fasting TG had a negative but insignificant correlation with HDL-C in these women.

Discussion

Hyperlipidemia is considered a risk factor for arteriosclerotic diseases. Examination of lipid profiles in aged women shows that TC rapidly increases to a higher level in these women than in men once they are over the age of 50, which is the average age at onset of menopause. In women, HDL-C remains uniform up to

Table 2 Fasting lipid profiles of four groups by triglyceride (TG) classification (mean ± SD)

Group	Age (years)	BMI (kg/m^2)	TG (mg/dL)	HDL-C (mg/dL)		LDL-C (mg/dL)	TC (mg/dL)		Arteriosclerosis index (TC-HDL)/HDL
Normotriglyceridemia† ($n = 36$)	52.3 ± 7.0	21.6 ± 2.4	87 ± 26	70 ± 15		150 ± 26	237 ± 26		2.5 ± 0.7
Mild postprandial hypertriglyceridemia ($n = 27$)	55.4 ± 7.0	21.6 ± 2.6	100 ± 29	64 ± 14	*	148 ± 32	230 ± 32	*	2.9 ± 1.0
Moderate postprandial hypertriglyceridemia ($n = 19$)	54.8 ± 7.2	22.0 ± 2.0	106 ± 26	52 ± 10		134 ± 36	212 ± 45		3.5 ± 0.8
Hypertriglyceridemia ($n = 9$)	58.4 ± 12.3	23.3 ± 2.9	229 ± 52	45 ± 9		118 ± 28	209 ± 24		3.8 ± 0.8

*$P < 0.01$.
†We defined normal triglyceridemia as fasting TG < 150 mg/dL using 225 mg/dL as the cut-off value for postprandial hypertriglyceridemia.
BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC-HDL, total cholesterol high-density lipoprotein.

the age of approximately 50, and then decreases slightly from then on, while TG concentration increases from the age of approximately 30 and peaks at the age of approximately 60. Therefore, in postmenopausal women, lipid metabolism declines with age and is characterized by an increase in TC, a decrease in HDL, and an increase in TG associated with a rapid decrease in the estrogen concentration.

When the circulating estrogen concentration falls after menopause, the number of LDL receptors in the liver decreases and LDL remains in the blood.[9] It is believed that the associated increase in TG concentration decreases the size of LDL particles, which promotes the progression of arteriosclerosis.[10] In this regard, it is reported that hormone replacement therapy (HRT) not only improves lipid metabolism but also exerts many anti-arteriosclerotic effects, such as antioxidant and vasodilatory effects. Binding estrogen (conjugated equine estrogen) not only produces desirable effects on lipid metabolism, it is also thought to induce hypertriglyceridemia.[3] Therefore, when starting HRT, lipid metabolism status needs to be assessed and patients with abnormalities need to be individually evaluated.

TC and LDL-C are recognized as risk factors for ischemic heart disease.[7] However, based on the Framingham Study,[11] HDL-C and TG are identified as more important risk factors for ischemic heart disease in postmenopausal women. In recent years, the concept of the metabolic syndrome as a high-risk pathology that causes arteriosclerotic diseases has also been put forward, and diagnostic criteria for this syndrome have been established.[12] The diagnostic criteria for the metabolic syndrome are the accumulation of visceral fat and the presence of at least two of the following factors: abnormal lipid metabolism, hypertension and abnormal glucose metabolism. Abnormal lipid metabolism is defined as TG concentrations ≥150 mg/dL or HDL-C concentrations <40 mg/dL.[12] Hypertriglyceridemia and a low blood HDL-C concentration are therefore specified in the diagnostic criteria together.[13,14] Patients with type 2 diabetes mellitus who have postprandial hypertriglyceridemia are reported to have a significant thickening of the vascular walls.[15] This abnormal condition suggests that there is also a correlation between abnormal lipid metabolism, including hypertriglyceridemia, and abnormal glucose metabolism (insulin resistance), which are included in the diagnostic criteria for the metabolic syndrome.

Postprandial TG concentration is markedly affected by food intake and needs to be viewed as a factor

that varies considerably with diet.[14,16] Even in adults without ischemic heart disease risks, it is believed that an association exists between chronic hypertriglyceridemia and increases in plasma concentrations of biochemical markers of inflammation and endothelial activation.[7] Postprandial TG concentration is higher in women with ischemic heart disease,[17] indicating that postprandial hypertriglyceridemia is an important risk factor for arteriosclerosis and ischemic heart disease. A study showed that postprandial (non-fasting) TG concentration is an independent predictor of ischemic heart disease and is of greater clinical significance than the fasting TG concentration.[8] A subanalysis of the same study also showed that the association between TG and ischemic heart disease was not substantially affected by TC or HDL-C concentrations, suggesting that postprandial TG has an independent role in ischemic heart disease risk.[8] This is because the TG concentration is said to peak at 6–8 h postprandially, and persists for much of the day.[18,19]

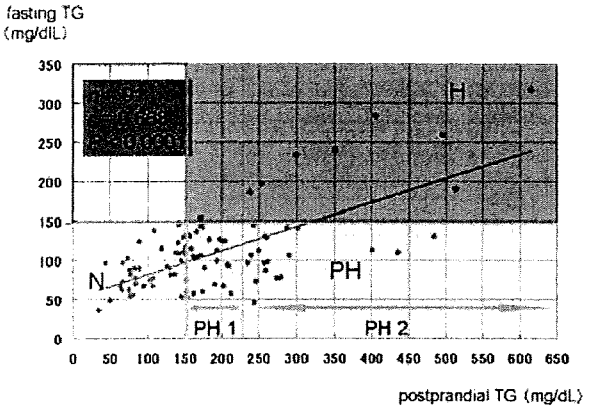

Figure 1 Relationship between postprandial triglycerides (TG) and fasting TG concentrations. H, hypertriglyceridemia (fasting TG ≥ 150 mg/dL); N, normotriglyceridemia (fasting TG < 150, postprandial TG < 150 mg/dL); PH 1, mild postprandial hypertriglyceridemia (fasting TG < 150, postprandial TG ≥ 150, <225 mg/dL); PH 2, moderate postprandial hypertriglyceridemia (fasting TG < 150, postprandial TG ≥ 225 mg/dL).

Postprandial (nonfasting) TG concentration is approximately 50% higher than the fasting TG concentration. Therefore, we consider 225 mg/dL an appropriate cut-off value for postprandial hypertriglyceridemia in those with a normal fasting TG concentration below 150 mg/dL. In our study, 46 of the 91 subjects, or approximately 50% of all subjects, had a high postprandial TG concentration (≥150 mg/dL) despite having a normal fasting TG concentration (Fig. 1). Through comparison of the four groups by using a postprandial TG concentration of 225 mg/dL as the cut-off value, we showed a significant difference in TC and HDL-C concentrations between the moderate postprandial hypertriglyceridemia group and the normotriglyceridemia group only. Furthermore, HDL-C negatively correlated with the postprandial TG concentration. Thus, postprandial TG could provide a better understanding of lipid metabolism.

The prevalence of postprandial hypertriglyceridemia in postmenopausal women is high. When starting HRT, it is also important to determine how to avoid adverse cerebrovascular effects. By changing the route of administration of estrogen preparations from oral to transdermal and by reducing the estrogen dose, an increase in TG or inflammation markers can be inhibited. It has also

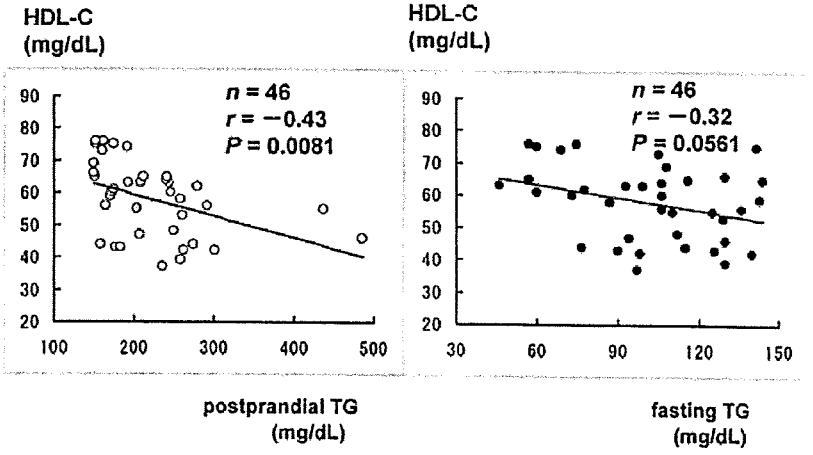

Figure 2 Correlation between high-density lipoprotein cholesterol (HDL-C) and postprandial or fasting triglyceride (TG) concentration in women with postprandial hypertriglyceridemia. Among the 46 women with postprandial hypertriglyceridemia, we found a significant negative correlation between their postprandial TG and their HDL-C ($r = -0.43$, $P = 0.0081$).

been found that progestin preparations not only reduce HDL-C but also inhibit vascular endothelial function, while natural progestin preparations have no such effects. Individual methods of administration therefore need to be investigated according to the characteristics of each HRT prescription.

In conclusion, we showed a high incidence of postprandial hypertriglyceridemia among postmenopausal women, and postprandial hypertriglyceridemia negatively correlated with HDL-C. Therefore, we conclude that postprandial TG could provide a better understanding of lipid metabolism. Measuring this parameter should be of value and may be used to screen postmenopausal women undergoing HRT so as to reduce cerebrovascular risks.

References

1. Manson JE, Hsia J, Johnson KC *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349**: 523–534.
2. Moorthy K, Yadav UC, Mantha AK *et al.* Estradiol and progesterone treatments change the lipid profile in naturally menopausal rats from different age groups. *Biogerontology* 2004; **5**: 411–419.
3. Murano T, Izumi S, Kika G *et al.* Impact of menopause on lipid and bone metabolism and effect of hormone replacement therapy. *Tokai J Exp Clin Med* 2003; **28**: 109–119.
4. Schlegel W, Petersdorf LI, Junker R, Schulte H, Ebert C, Von Eckardstein A. The effects of six months of treatment with a low-dose of conjugated oestrogens in menopausal women. *Clin Endocrinol* 1999; **51**: 643–651.
5. Sieminska L, Wojciechowska C, Niedziolka D *et al.* Effect of postmenopause and hormone replacement therapy on serum adiponectin levels. *Metabolism* 2005; **54**: 1610–1614.
6. Capell WH, DeSouza CA, Poirier P *et al.* Short-term triglyceride lowering with fenofibrate improves vasodilator function in subjects with hypertriglyceridemia. *Arterioscler Thromb Vasc Biol* 2003; **23**: 307–313.
7. Lundman P, Eriksson MJ, Silveira A *et al.* Relation of hypertriglyceridemia to plasma concentrations of biochemical markers of inflammation and endothelial activation (C-reactive protein, interleukin-6, soluble adhesion molecules, von Willebrand factor, and endothelin-1). *Am J Cardiol* 2003; **91**: 1128–1131.
8. Iso H, Naito Y, Sato S *et al.* Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol* 2001; **153**: 490–499.
9. Arca M, Vega GL, Grundy SM. Hypercholesterolemia in postmenopausal women. Metabolic defects and response to low-dose lovastatin. *JAMA* 1994; **271**: 453–459.
10. Ikenoue N, Wakatsuki A, Okatani Y. Small low-density lipoprotein particles in women with natural or surgically induced menopause. *Obstet Gynecol* 1999; **93**: 566–570.
11. Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J* 1986; **112**: 432–437.
12. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; **366**: 1059–1062.
13. Creatsas G, Christodoulakos G, Lambrinoudaki I. Cardiovascular disease: screening and management of the a-symptomatic high-risk post-menopausal woman. *Maturitas* 2005; **52**: S32–37.
14. Halkes CJ, Castro Cabezas M, van Wijk JP, Erkelens DW. Gender differences in diurnal triglyceridemia in lean and overweight subjects. *Int J Obes Relat Metab Disord* 2001; **25**: 1767–1774.
15. Chen X, Tian H, Liu R. Association between fasting and postprandial triglyceride levels and carotid intima-media thickness in type 2 diabetes patients. *Chin Med J* 2003; **116**: 1933–1935.
16. Tanaka A, Tomie N, Nakano T *et al.* Measurement of postprandial remnant-like particles (RLPs) following a fat-loading test. *Clin Chim Acta* 1998; **275**: 43–52.
17. Kofoed SC, Gronholdt ML, Bismuth J, Wilhjelm JE, Sillesen H, Nordestgaard BG. Echolucent, rupture-prone carotid plaques associated with elevated triglyceride-rich lipoproteins, particularly in women. *J Vasc Surg* 2002; **36**: 783–792.
18. Pirro M, Lupattelli G, Siepi D *et al.* Postprandial lipemia and associated metabolic disturbances in healthy and hyperlipemic postmenopausal women. *Metabolism* 2001; **50**: 330–334.
19. Tsunoda F, Koba S, Hirano T *et al.* Association between small dense low-density lipoprotein and postprandial accumulation of triglyceride-rich remnant-like particles in normotriglyceridemic patients with myocardial infarction. *Circ J* 2004; **68**: 1165–1172.

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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.

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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 pub-

lished 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), crosslinked 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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References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. (1993) Am J Med 94:646–650
2. NIH consensus development panel on osteoporosis prevention, diagnosis, and therapy. Osteoporosis prevention, diagnosis, and therapy. (2001) JAMA 285:785–795
3. 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 osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
4. Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
5. WHO Scientific Group on the Prevention and Management of Osteoporosis (2000) Prevention and management of osteoporosis: report of a WHO Scientific Group, Geneva, PA. World Health Organization, Geneva, pp 1–3
6. Sasaki S, Yanagibori R (2001) Association between current nutrient intakes and bone mineral density at calcaneus in pre-and postmenopausal Japanese women. J Nutr Sci Vitaminol 47:289–294
7. Nordin BE (1997) Calcium and osteoporosis. Nutrition 13:664–686
8. Valimaki MJ, Karkkaine M, Lamberg-Allardt C, Laitinen K, Alhaa E, et al. (1994) Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass. Cardiovascular Risk in Young Finns Study Group. BMJ 23;309(6949):230–235.
9. Cooper C, Cawley M, Bhalla A, Egger P, Ring F, Morton L, Barker D (1995) Childhood growth, physical activity, and peak bone mass in women. J Bone Miner Res 10:940–947
10. Uusi-Rasi K, Sievanen H, Vuori I, Pasanen M, Heinonen A, Oja P (1998) Associations of physical activity and calcium intake with bone mass and size in healthy women at different ages. J Bone Miner Res 13:133–142
11. Hirota T, Kusu T, Hirota K (2005) Improvement of nutrition stimulates bone mineral gain in Japanese school children and adolescents. Osteoporosis Int 16:1057–1064
12. Takada K (2004) Bone mass and lifestyle-effect of exercise and nutrition (in Japanese). Clin Calcium 14:1684–1695
13. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, et al. Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
14. Sasaki S, Ushio F, Amano K, Morihara M, Todoriki T, Uehara Y, Toyooka T (2000) Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. J Nutr Sci Vitaminol 59:285–296
15. Harada A, Naito Y, Inoue S, Kitabatake Y, Arao T, Ohashi Y, JALS Group (2003) Validity of a questionnaire for assessment of physical activity in the Japan Arteriosclerosis Longitudinal Study. Med Sci Sports Exerc 35(suppl 1):S340
16. Babaroutsi E, Magkos F, Manios Y, Sidossis LS (2005) Body mass index, calcium index, and physical activity affect calcaneal in healthy Greek males in an age-dependent and parameter-spcific manner. J Bone Miner Metab 23:157–166
17. Yoshimura N (2003) Exercise and physical activities for the prevention of osteoporotic fractures: a review of the evidence (in Japanese). Nippon Eiseigaku Zassi (Jpn J Hyg) 58:328–337
18. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD (1997) Prospective ten-month exercise intervention in premenarcheal girls: positive effects on bone and lean mass. J Bone Miner Res 12:1453–1462
19. Bradney M, Pearce G, Naughton G, Sullivan C, Bass S, Beck T, Carlson J, Seeman E (1998) Moderate exercise during growth in prepubertal boys: changes in bone mass, size volumetric density and bone strength: a controlled prospective study. J Bone Miner Res 13:1814–1821
20. Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, Seeman E (1998) Exercise before puberty may confer residual benefits in bone density adulthood: studies in active pre-pubertal and retired female gymnasts. J Bone Miner Res 13:500–507
21. Devine A, Dhaliwal SS, Dick IM, Bollerslev J, Prince RL (2004) Physical activity and calcium consumption are important determinants of lower limb bone mass in older women. J Bone Miner Res 19:1634–1639
22. Welten DC, Kemper HCG, Post GB, van Staveren WA (1995) A meta-analysis of the effect of calcium intake on bone mass in young and middle aged females and males. J Nutr 125:2802–2813
23. Cumming RG, Nevitt MC (1997) Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 12:1321–1329
24. Xu L, McElduff P, D'Este C, Attia J (2004) Does dietary calcium have a protective effect on bone fracture in women? A meta-analysis of observational studies. Br J Nutr 91:625–634

特集
各診療科における漢方医学からみたアンチエイジング

特集によせて

漢方医学とアンチエイジング

―メタボリックシンドロームを中心に―

太田　博明

1．漢方医学と現代医学

中国の古典にも記載されているように，漢方医学では「未病を治す」ということが一つの大きな特徴である。この「未病を治す」とは単純に「病気にならないようにする」ことであり，いいかえれば，疾病が完成しないうちに初期症状に注目して治療することである。これら予防医学的な側面とともに早期発見・早期治療を意味し，現代医学にも通じる考え方である。

最近，インフルエンザが流行しているが，いくら流行してもかかる人とかからない人がおり，この差は体力や疲労度，また環境などが関与するものと思われるが，内部環境を整えれば外部からの影響を受けない，病気には罹患しないというのが未病の発想である。特に近代化以前は，人類は感染症との戦いであったので，病因が判らない以前は内部環境の整備が特に重要であったことは良く理解できる。

一方，もう一つの「未病を治す」意としての早期発見・早期治療は現代医学においても重要視されている。因みに，1956年，わが国の3大死因の癌，脳卒中，心臓病を「成人病」とし，検診の普及を図った結果，早期発見・早期治療としての実が挙がった[1]ことはよく知られている。漢方医学における「未病を治す」意義はこのように現代医学においても勿論，相通ずるものがある。すなわち，現代医学においては昨年4月よりメタボリックシンドローム（Met-s）を標的とした特定健診・特定保健指導が行われているが，これがまさに「未病を治す」に該当する。

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表1　8学会*合同委員会によるメタボリックシンドロームの診断基準

2005年

腹腔内脂肪蓄積	
ウエスト周囲径 （内臓脂肪面積　男女とも≧ 100cm^{2}に相当）	男性 ≧ 85 cm 女性 ≧ 90 cm
上記に加え以下のうち2項目	
高トリグリセリド血症 かつ/または 低HDLコレステロール血症	≧ 150mg/ dL ＜40mg/ dL 男女とも
最高（収縮期）血圧 かつ/または 最低（拡張期）血圧	≧ 130 mmHg ≧ 85 mmHg
空腹時高血糖	≧ 110mg/ dL

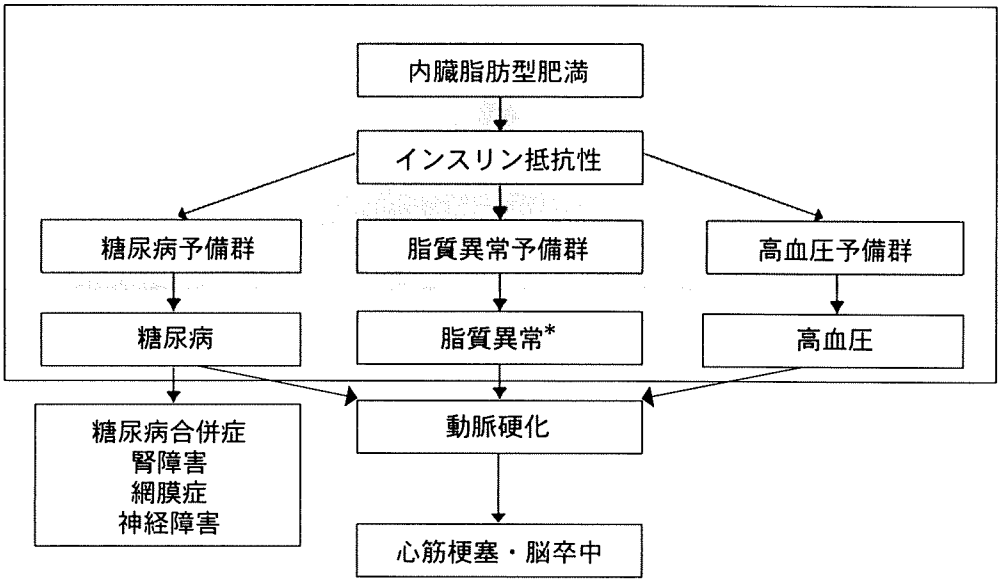
*日本動脈硬化学会、日本糖尿病学会、日本高血圧学会、日本肥満学会
日本循環器学会、日本腎臓学会、日本血栓止血学会、日本内科学会

2. 加齢による肥満とメタボリックシンドローム

近年，わが国においては，若い女性の「やせ」が医学的にも社会的にも問題となっている。しかし，節制を重ねている女性も60歳を超えると，BMI 25以上の肥満者の割合が急に増加し，Met-sに傾き，各種生活習慣病発症の契機[2]となっている。脂肪分解はβ_3アドレナリン（AR）が関与するといわれ，エストロゲン分泌が低下すると内臓脂肪におけるβ_3ARの受容体発現量が低下し，内臓脂肪が蓄積し，閉経後期間とともにそれが加速する[3]ことによって，加齢とともに閉経後10年，60歳位からMet-sを呈するようになる。

Met-sとは，わが国の8学会合同委員会による2005年の診断基準[4]によると，内臓脂肪蓄積100cm^{2}以上の脂肪蓄積に加え，高トリグリセリド血症（≧150mg/dL），低HDLコレステロール血症（＜40mg/dL）のいずれかもしくは両方，または最高（収縮期）血圧（≧130mmHg），最低（拡張期）血圧（≧85mmHg）のいずれかもしくは両方，または空腹時高血糖（≧110mg/dL）の3項目のうち，2項目に該当する場合とされている（表1）。内臓脂肪型肥満はインスリン抵抗性が高まり，糖尿病，脂質異常，高血圧の予備群となる（図1）。これらの予備群がこの度の特定保健指導が主たる標的とする部分である。この予備群は表1の基準から，各種の程度があり，漢方医学から「未病を治す」という範疇に入るものである。これらの予備群はやがて予備群の域を超え，本格的な糖尿病，脂質異常症，高血圧へと進展し，疾病は確立し，保健指導の域

メタボリックシンドロームの病態



*脂質異常に総コレステロールまたはLDLコレステロールが含まれていないことに注意
部分が特定保健指導が主たる標的とする部分

図1

を超えるわけである。この3疾患においても各々軽度から，中等度，高度と幅広い病態があり，病態により保健指導に加え，各種の薬物介入を要することとなる。

これらのある程度以上の糖尿病，脂質異常症，高血圧は放置し続けたり，治療が奏効せず，ある程度以上の期間その状態が持続することにより，血管内皮の機能障害を呈する。各種要因により内皮機能障害を呈するが，それによってNO産生の低下，炎症性サイトカインの産生亢進，接着因子の発現亢進などが複合的に関与し，動脈硬化の発生となる（図2）。動脈硬化の初期段階においては機能的変化のみ出現し，やがて器質的変化の出現となり，器質的変化はさらに進展し，臓器障害の出現となる（図3）。これらの過程により，臓器障害の終末像として，脳卒中・心筋梗塞などのいわゆるイベント発生となる。以上のごとく，Met-sが進展すると動脈硬化を発症することとなり，ここからはMet-sの枠を超えた，いわゆる生活習慣病の端緒となり，生活習慣病の終末像が脳卒中，心筋梗塞のイベント発生である。

3. メタボリックシンドロームの治療と漢方医学

Met-sの中核をなす病態は糖尿病，脂質異常症，高血圧であり，各々血液検査の結果をもとに病態を把握し，抗糖尿病薬やインスリン，脂質低下薬，降圧薬によって薬剤介入を行うのが現代医学による西洋医学である。しかし，Met-sの源流となる内臓

内皮機能障害と動脈硬化の発生・進展

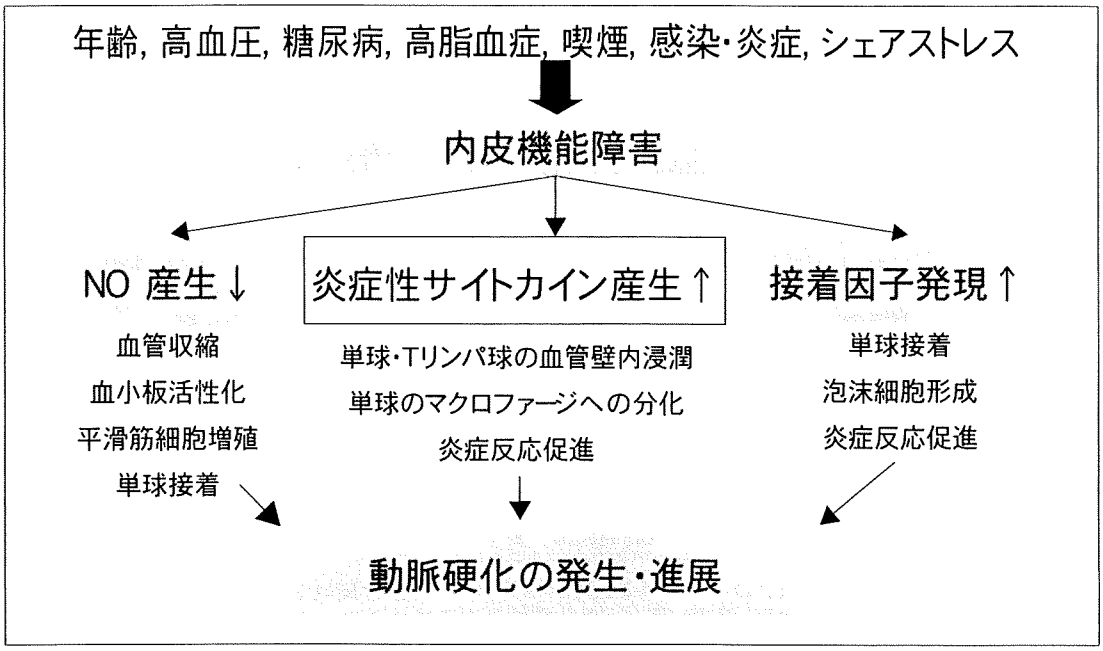


図2

動脈硬化の進展とその評価法

松尾　汎　Mebio 2005 改変

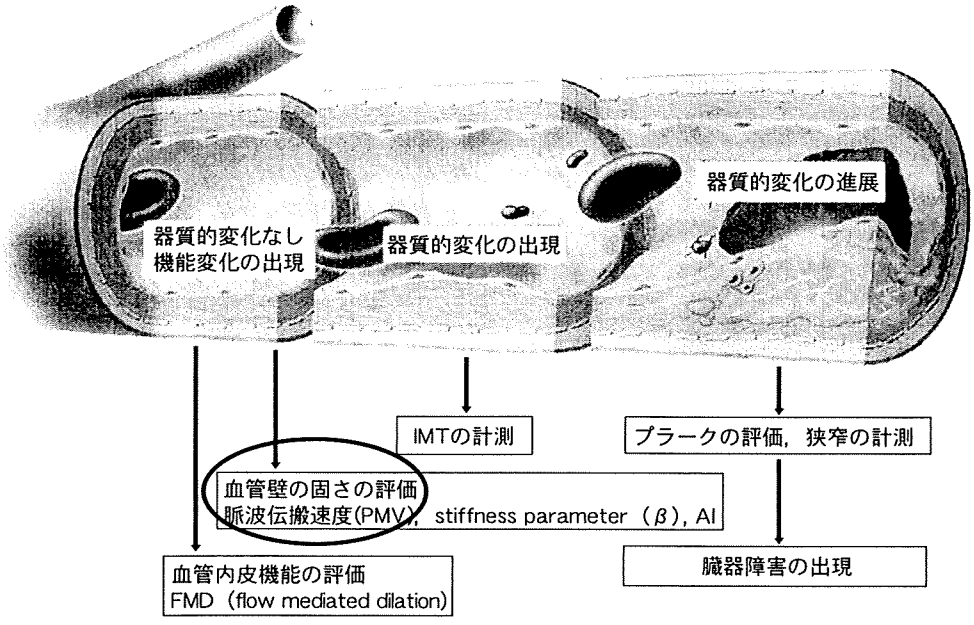


図3

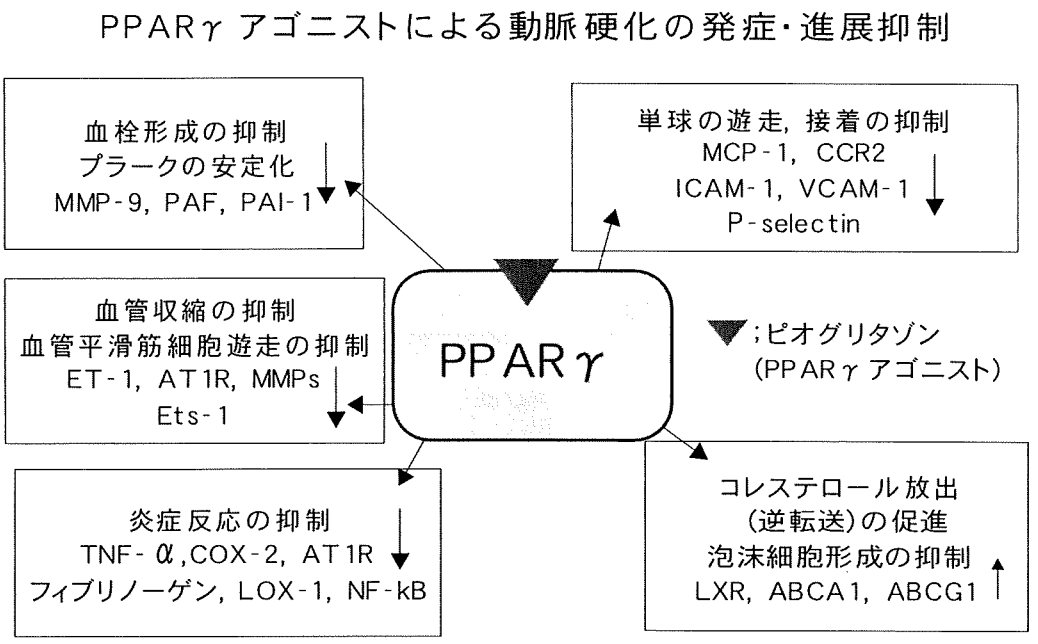


図4

脂肪の蓄積と，それに伴うインスリン抵抗性であるが，西洋医学の立場からも世界中でその治療薬の創薬活動が行われているが，現在のところ肥満そのものに対しては臨床応用にまだ達する状況にはない。西洋医学には抗肥満薬として唯一マシンドールがあるが，特殊な目的以外には適応されず，現在，西洋医学的に内臓肥満に対応できる薬物療法はない状態である。

但し，西洋医学にも肥満による炎症やインスリン抵抗性に対して，転写因子であるPPARγ agonistである経口糖尿病薬のピオグリタゾンがPPARγの活性化を直接的に促進するといわれている。しかし，このピオグリタゾンは図4のごとく，単球の遊走，接着の抑制，血栓形成の抑制，プラークの安定化，血管収縮の抑制，血管平滑筋細胞の遊走抑制，炎症反応の抑制，コレステロール放出（逆転送）の促進，泡沫細胞形成の抑制など，各種要因による動脈硬化の発症・進展抑制を目指した治療薬剤であり，抗肥満薬剤ではない。事実，図5のごとくピオグリタゾン36ヵ月投与により，HbA_{1c}，トリグリセリドの有意な低下とHDL-Cの有意な上昇が認められ，糖代謝と脂質代謝低下作用が示されている。

一方，漢方医学には肥満に対して効果が期待できるものとして防風通聖散と防已黄耆湯がある。漢方医学的には肥満は過食による「食毒」や水分代謝が滞った「水毒」，および月経，妊娠，分娩，更年期などの女性ホルモンの変動や冷えに伴う血液の停滞，すなわち「瘀血」などが原因となって起こると考えられている。またイライラな