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

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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

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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]

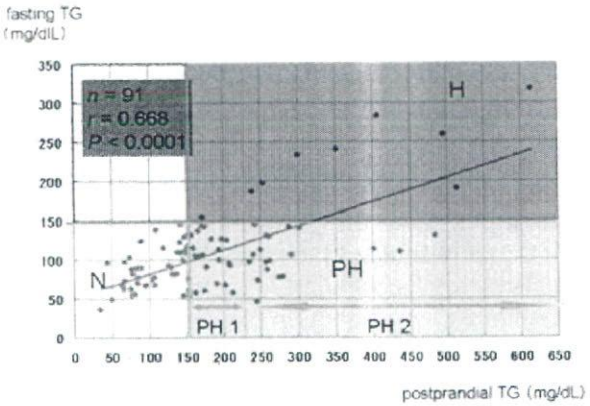

Figure 1 Relationship between postprandial triglycerides (TG) and fasting TG concentrations. H, hypertriglyceridemia (fasting TG ≥ 150 mg/dL); N, normotriglyceridemia (fasting TG < 150, postprandial TG < 150 mg/dL); PH 1, mild postprandial hypertriglyceridemia (fasting TG < 150, postprandial TG ≥ 150,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

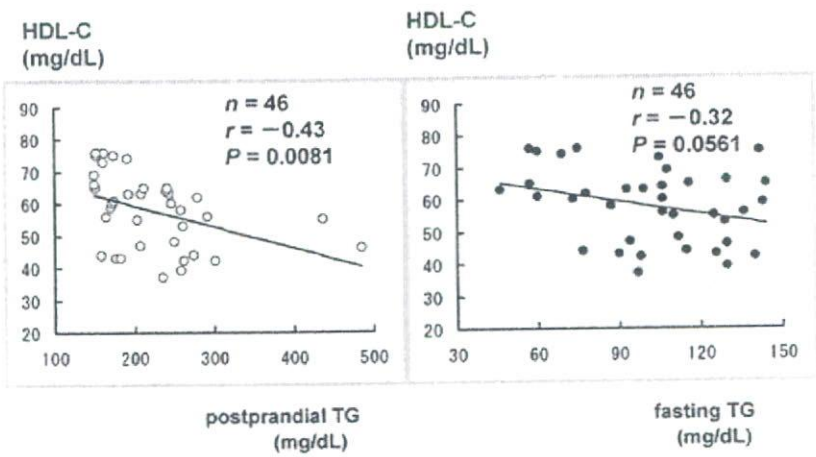

Figure 2 Correlation between high-density lipoprotein cholesterol (HDL-C) and postprandial or fasting triglyceride (TG) concentration in women with postprandial hypertriglyceridemia. Among the 46 women with postprandial hypertriglyceridemia, we found a significant negative correlation between their postprandial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

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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.

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Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women

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ABSTRACT

It was reported that low bone mineral density (BMD), osteoporotic fractures and low serum 25-hydroxyvitamin D (25-OHVD) levels increase the risk of mortality in elderly Caucasian people. However, there is no data available on the relationship between bone mineral density or 25-OHVD levels and mortality in elderly Asian women. To determine whether or not low bone mineral density (BMD) or low 25-OHVD levels contribute to increased mortality risk, we conducted a prospective observational study in 1232 ambulatory postmenopausal female volunteers. Information was obtained from the subjects on baseline BMD, the serum levels of biochemical indices including 25-OHVD, prevalent fractures, co-morbidities and lifestyle variables. The participants were observed for a total of 6.9±3.6 years (mean±SD) and a total of 107 participants (8.7%) were dead during the observation. Mortality was assessed and confirmed on the certificates or hospital records or information from their family. In addition to traditional risks for mortality, such as age (Hazard ratio, 1.73, 95% CI, 1.51–1.98, $P<0.01$), 25-OHVD level <50 nmol/l (HR 2.17, 1.27–3.72, $P=0.01$), prevalent malignancies (HR 5.60, 3.36–9.31, $P<0.01$) and existing osteoporosis (HR 2.14, 1.22–3.75, $P=0.01$) were found to be significant independent risk factors for all-cause mortality by using multivariate Cox's regression analysis. It is suggested that prevalent osteoporosis, prevalent malignancy or lower levels of 25-OHVD represent powerful risk factors for mortality.

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Introduction

Osteoporosis as it is characterized by deteriorated bone strength [1] is a national burden in our aging society because of its high susceptibility to bone fractures, which could result in the impaired quality of life of affected patients [2–4]. Fractures are also known to associate with increased morbidity and mortality [5–9]. The increase in mortality after femoral neck fractures has been well documented both in the Caucasian [5,6,10–12] and the Asian populations [13]. In addition to femoral neck fractures, vertebral fractures have been reported to be a risk factor for mortality in the Caucasian population [5,8,10,14]. The phenotypes of osteoporosis accounted for by factors other than fractures, such as low bone mineral density [15,16] or bone density and weight loss [17], were also reported to be associated with mortality. However, the association between the osteoporotic phenotypes and mortality has not been fully investigated in the Asian population. Therefore, the first primary aim of the present study is to clarify whether BMD or fractures correlated with mortality in postmenopausal Japanese women.

The cause of excess mortality in osteoporosis is not understood well. Co-morbidities [5] and frailty [18] were postulated to be causes of high mortality in osteoporosis. However, it is unclear which type(s) of co-morbidities present contributes to increased mortality in osteoporosis. Thus, the secondary aim of the present study is to investigate which of the co-morbidities present is associated with high mortality in osteoporosis.

Recent studies indicated that the serum level of 25-hydroxyvitamin D (25-OHVD) was associated with low BMD or fractures [19,20] and low level of 25-OHVD was shown to be associated with falling [21,22], which is a major cause of fractures [23] and a typical sign of frailty in elderly people. Furthermore, it is reported that low 25-OHVD levels are associated with a greater future risk of nursing home admission and possibly mortality [24]. The third aim of the present study was therefore to examine whether a low baseline serum level of 25-OHVD was associated with mortality in postmenopausal Japanese women.

To address these issues, we conducted the prospective study in Japanese postmenopausal women.

Methods and subjects

Subject selection

This study was a prospective observational study started from 1 April 1993 in Nagano prefecture, Japan. Study participants included ambulatory postmenopausal

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volunteers over 40 years old who were recruited from clinical visiting patients. The exclusion criteria included: critical illness, bed bound, and irregular clinical visit. The baseline examinations were conducted in the subjects after their informed consent to this longitudinal study was obtained. The period of follow-up for each participant was calculated as the time from inclusion in the study to the occurrence of death, lost to follow-up, or the endpoint reached in 30 April 2007. The present study included only those who were followed for more than one year.

Medical history taking at baseline

As the baseline examination, body weight and height were measured, an interview was carried out on their smoking habit, alcohol drinking, and histories of co-morbidities including diabetes mellitus, hypertension, dyslipidemia, dementia, malignancy, and cardio- and cerebrovascular events. When the subject indicated some co-morbidity, the diagnosis of that co-morbidity was made as the following: *diabetes mellitus*, defined as a spot level of blood glucose over 200 mg/dl or HbA1c in excess of 6.5% or the subjects receiving anti-diabetic drugs as confirmed on medical history taking [25]; *hypertension*, defined as those who met the diagnostic criteria for hypertension as proposed by the Japanese Society of Hypertension, in other words, those whose systolic and diastolic blood pressure was above 140 and 90 mmHg or those who were given anti-hypertension drug or diagnosed as having hypertension [26]; and *dyslipidemia*, defined as those with hypercholesterolemia (≥220 mg/dl) and/or hypertriglyceridemia (≥150 mg/dl in the fasting state), diagnosed as having dyslipidemia [27]. When non-fasting spot serum samples indicated that the serum triglycerides exceeded 200 mg/dl, or the serum total cholesterol exceeded 220 mg/dl, fasting serum samples were obtained in order to confirm the presence or absence of dyslipidemia. The subjects were examined in the course of interview for the presence or absence of dementia, malignancies, or a cardio- and cerebrovascular event.

Measurements of BMD

Axial BMD (lumbar spine (LBMD)) was measured by dual-energy X-ray absorptiometry (DXA) using a Lunar DPX-L or DPX-IQ (Lunar Corporation, Madison, WI, USA). The inter-assay variance of LBMD in our laboratory was 0.5± 0.5% (CV±SD) [28]. To detect machine drift, a quality assurance test was carried out at every measurement.

Measurements of biochemical indices

Non-fasting serum, plasma and urine samples were collected at the time of enrollment as baseline data. Serum samples were centrifuged and stored at −20° until measurement. Serum 25-OHVD was measured at every 2 to 3 months interval by using a competitive protein-binding assay after extraction and purification of the samples using HPLC [29] at Teijin Bio Science Laboratories (Hino, Tokyo, Japan) blinded to their subject identity. The C/V for inter-assay variance of 25-OHVD was calculated as 12.5± 1.2% for the range of 5–50 ng/ml of 25-OHVD (n=50). Serum 25-OHVD was classified into four groups using the following cutoffs: <25.0 nmol/l for deficiency, 25.0–49.9 nmol/l for insufficiency, 50.0–74.9 nmol/l for borderline, and >75 nmol/l for normal [24]. Other routine biochemical examinations such as serum and urinary levels of calcium and creatinine, serum levels of total protein, Al-P activity, inorganic phosphate, total cholesterol, creatinine, triglycerides, HbA1c and blood glucose, were analyzed immediately. Glomerular filtration rate (GFR) was calculated from creatinine, age and body size as a parameter of renal function. The formula for GFR was calculated as follows [30]: GFR (ml/min/1.73 m^2)=0.881×186.3×S−$Cr^{-1.154}$×$Age^{-0.203}$×0.742.

GFR was classified into five groups on the basis of published cutoffs: <15.0 ml/min/1.73 m^2 for stage 5, 15.0–29.0 ml/min/1.73 m^2 for stage 4, 30.0–59.9 ml/min/1.73 m^2 for stage 3, 60.0–89.9 ml/min/1.73 m^2 for stage 2, and >90.0 ml/min/1.73 m^2 for stage 1 [31].

Diagnosis of osteoporosis and treatment

The diagnosis of osteoporosis was made in accordance with the diagnostic criteria for osteoporosis (2000 version) proposed by the Japanese Society for Bone and Mineral Research [32] where osteoporosis is diagnosed as the presence of fragility fractures in any bone lesion in those with BMD less than 80% (−1.63 SD) of the young adult mean (YAM). Osteoporosis is also diagnosed when the LBMD is less than 70% (−2.45SD) of the YAM even in those without prevalent fragility fracture. In those diagnosed as having osteoporosis, bone resorption inhibitors (bisphosphonate or estrogen), 1-alpha-OH vitamin D3 or vitamin K2 were administered if they desired to receive treatment. The specific treatment given to each of these subjects was selected in accordance with her preference with our assistance. Some of the patients with osteoporosis did not want to receive any osteoporotic drugs for a variety of reasons and some patients showed very low compliance to the therapeutic regimen prescribed. Therefore, the subjects were categorized into three groups by treatment: no treatment, bisphosphonate or estrogen and vitamin groups.

Definition of prevalent fracture

Whether prevalent fractures of vertebral and long bone (fractures of the femoral neck, distal end of radius, surgical neck or other sites of long bone) were associated with mortality or not, was investigated. Vertebral fractures were diagnosed by a semi-quantitative visual method [33]. The presence of prevalent long bone fractures was determined during the course of interviews with the participants or on the basis of the medical records or was confirmed on X-ray films.

Assessment of mortality

The death or survival of the study participants was confirmed at their last visit in April 2007. An attempt was made to contact those who did not show up by telephone or letter recommending their visit to the clinic and their death or survival was confirmed through inquiry. Those subjects who lost contact or never responded were treated as missing cases. Those who were followed up for more than 1 year before they lost touch were incorporated into subsequent analyses. The date of death was confirmed on the basis of the death certificates or hospital records available. Some of the participants were confirmed as having been dead by their family, in which cases the reported cause of their death was thought to be inaccurate. Thus, analysis of the causes of the participants' death included cases in which the accurate causes were not known. We also had lost contact with those subjects who moved to nursing homes or to their relative's due to loss of their independency in daily living. The follow-up of these subjects was terminated upon confirmation that they moved.

Ethical considerations

The protocol of the present study was reviewed by the ethical committee of the Research Institute and Practice for Involutional Diseases (RIPID), and detailed written informed consent was obtained from all the subjects.

Statistical analysis

In the descriptive analysis of the baseline characteristics, the numerical data are expressed as mean±SD. The age categories were tested for baseline differences by using ANOVA or chi-square test. Cox's proportional hazards model was used to estimate the association and time dependency between the baseline indices and death as an endpoint. Hazard ratios with 95% confidence intervals for selected variables are reported. First, we estimated the age-adjusted hazard ratios with 95% confidence intervals for study variables. Second, in multivariate Cox's regression analysis, we used the backward variable selection method. The exclusion criterion was a P-value of less

Table 1
Baseline characteristics of the study participants by age category

Characteristic	Age category (years)			P
	<60	60–69	≥70	
Participants (n, %)	443, 36.0	372, 30.2	417, 33.8	
BMI (%)				
<18.5 kg/m2	2.3	2.2	5.1	
18.5–25 kg/m2	27.4	21.8	23.5	<0.01
≥ 25.0 kg/m2	6.3	6.3	5.3	
25-OHVD (%)				
<25 nmol/l	0.5	0.9	1.2	
25–49.9 nmol/l	16.2	12.5	15.7	0.25
50.0–74.9 nmol/l	15.7	16.5	13.9	
≥75.0 nmol/l	2.5	2.5	1.9	
GFR (%)				
15–29.9 ml/min/1.73 m^2	0.1	0.1	0.3	
30.0–59.9 ml/min/1.73 m^2	8.3	10.4	11.7	
60.0–89.9 ml/min/1.73 m^2	17.7	11.2	14.7	<0.01
≥90.0 ml/min/1.73 m^2	9.7	8.6	7.3	
Smoking (yes%)	1.0	0.3	0.2	0.01
Alcohol drinking (yes%)	3.2	1.3	0.8	<0.01
Co-morbidities (%)				
Diabetes mellitus	1.1	1.7	2.3	0.04
Hypertension	8.5	11.5	21.2	<0.01
Hyperlipidemia	14.7	12.5	10.1	<0.01
Dementia	0.0	0.4	4.4	<0.01
Malignancy	2.0	2.1	3.5	<0.01
Cardiovascular events	1.1	2.7	7.8	<0.01
BMD category (%)				
Normal	20.5	8.4	6.5	
Osteopenia	8.1	7.7	5.7	<0.01
Osteoporosis	7.4	14.0	21.7	
Prevalent fracture (%)				
Vertebrae	0.8	5.8	13.8	<0.01
Long bone	1.0	1.1	2.8	0.01
Therapy pattern (%)				
No treatment	24.0	16.8	17.1	
Bisphosphonate or estrogen	9.7	8.5	7.3	<0.01
Vitamin	2.0	5.0	9.6	

BMI; body mass index, 25-OHVD; 25-hydroxyvitamin D, GFR; Glomerular filtration rate, BMD; bone mineral density.
P-value was tested by using ANOVA or chi-square.

Table 2
Age-adjusted hazard ratios for death by baseline parameter, Cox's hazard model

Item	Hazard ratio	95% CI		P
BMI (+1 kg/m^2)	0.95	0.89	1.01	0.10
25-OHVD (< 50 nmol/l/≥50 nmol/l)	1.54	1.22	1.97	<0.01
GFR (+1 stage)	1.20	0.93	1.57	0.16
Smoking (yes/no)	7.51	1.22	24.67	0.03
Alcohol drinking (yes/no)	2.92	1.02	6.54	0.04
Diabetes mellitus (yes/no)	1.31	0.88	2.20	0.21
Hypertension (yes/no)	1.24	10.1	1.52	0.04
Hyperlipidemia (yes/no)	1.13	0.90	1.44	0.29
Dementia (yes/no)	1.79	1.09	2.87	0.02
Malignancy (yes/no)	4.76	2.92	7.50	<0.01
Cardiovascular event (yes/no)	2.13	1.40	3.21	<0.01
Prevalent fracture (yes/no)	1.79	1.20	2.66	<0.01
Therapy pattern (BP+ES+V/no)	1.27	0.86	1.86	0.23
Therapy pattern (BP+ES/V+no)	0.68	0.36	1.20	0.19
BMD category (osteopenia/normal)	0.62	0.26	1.36	0.23
BMD category (osteoporosis/osteopenia)	3.09	1.62	6.65	<0.01

CI; Confidence interval, BMI; body mass index, 25-OHVD; 25-hydroxyvitamin D, GFR;. Glomerular filtration rate, BP; bisphosphonate, ES; estrogen, V; vitamin, BMD; bone mineral density.

than 0.2 and the missing values for 25-OHVD were imputed by using multiple imputation method [34]. Finally, Kaplan–Meier plots were shown by prognostic factors, with log-rank test. All the P-values presented are taken from the two-side test and were considered to be significant when they were less than 0.05. All the analyses were performed using the SAS software, Version 9.1 (SAS Institute Inc. Carly, NC, USA).

Results

In the 1232 women enrolled in this study, the mean and SD range of observational period was 6.9±3.6 years with the longest observation time being 14.0 years. Table 1 lists the baseline characteristics of the subjects. The mean and SD range for age of the participants at baseline was 63.9±10.5 years old (mean±SD). Vitamin D insufficiency and deficiency as evaluated by the baseline 25-OHVD level was found in 331 (44.3%) and 20 (2.7%) of the participants, respectively. Twenty subjects showed 25-OHVD levels suggestive of vitamin D deficiency with none showing obvious clinical signs and symptoms of osteomalacia. In contrast to the data reported for the Caucasian population, the subjects with smoking or alcohol habit were markedly fewer. A total of 531 (43.1%) subjects were diagnosed as having osteoporosis at baseline and the prevalence of osteoporosis in these subjects correlated with the advancing years as well as the presence of prevalent fracture. Prevalent vertebral or long bone fractures were observed in 294 (23.9%) subjects. A total of 107 subjects (8.7%) were dead during the observation that lasted until the end of April 2007. The median period of observation to their death was 5.3 years. The death rate was 12.6 deaths/1000 person-year. Survival was confirmed in a total of 790 (64.1%) who were censored on their last clinic visit. The remaining 335 participants (27.2%) were lost to follow-up through regular clinical visits during the observation period. Of the 335 participants lost to follow-up, 122 (9.9%) subjects were found to be bedridden or to have been admitted to nursing homes, with the remaining 213 (17.3%) lost to follow-up for

Table 3
Multivariate Cox's regression analyses of prognostic factors for death

Item	Hazard ratio	95% CI		P
Age (+5 year)	1.73	1.51	1.98	<0.01
25-OHVD (<50 nmol/l/≥50 nmol/l)	2.17	1.27	3.72	0.01
Smoking (yes/no)	4.29	0.81	22.80	0.09
Drinking (yes/no)	2.16	0.73	6.38	0.16
Cardiovascular event (yes/no)	1.48	0.93	2.36	0.09
Dementia (yes/no)	1.54	0.89	2.66	0.12
Malignancy (yes/no)	5.60	3.36	9.31	<0.01
BMD category (osteopenia/normal)	0.72	0.32	1.65	0.44
BMD category (osteoporosis/normal)	2.14	1.22	3.75	0.01

CI; Confidence interval, 25-OHVD; 25-hydroxyvitamin D, BMD; bone mineral density. Backward variable selection method with criterion P<0.2 is used to reduce model.

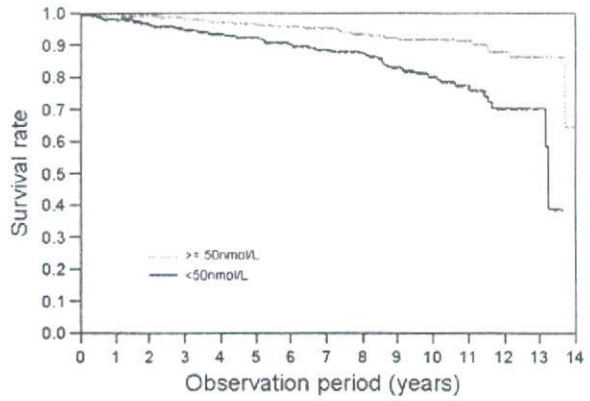

Fig. 1. Kaplan–Meier plots of survival by serum 25-hydroxyvitamin D level. 25-OHVD <50 nmol/l denotes deficiency and insufficiency; and ≥50 nmol/l, normal and borderline. There is a significant difference between the 25-OHVD categories (log-rank test; P<0.01).

unknown reasons. There was no difference in the rate of subjects lost to follow-up between those with osteoporosis and without (P=0.56). The causes of the subjects' death were vascular event (30 cases, 28.0%), cancer (23 cases, 21.5%), senile decay (23 cases, 21.5%), other (11 cases, 10.3%) and unknown (20 cases, 18.7%). Of the 30 subjects who died due to vascular events, 22 subjects (73.3%) had previous histories of cardio- or cerebrovascular events at baseline, and of the 23 who died of cancer, 16 (69.6%) had a history of malignancy, indicating that the remaining 8 and 7 deaths, respectively, due to vascular events and cancer, were incidental events during the observation. The subjects in the osteoporosis group showed a lower baseline prevalence of diabetes mellitus (3.2 versus 6.6%; P<0.01) and dyslipidemia (29.6 versus 43.3%; P<0.01) than those in the non-osteoporosis group. The baseline prevalence of hypertension (42.3 versus 40.4%) and cardio- or cerebrovascular events (12.9 versus 10.4%) in the osteoporosis group or non-osteoporosis group was not statistically significantly different (P>0.05). The baseline prevalence of and dementia was significantly higher in the osteoporosis group than those in the non-osteoporosis group (7.2 versus 2.9%; P<0.01). Meanwhile, there were no significant differences between osteoporosis and non-osteoporosis groups in baseline prevalence of malignancies (7.8 versus 7.6%; P>0.05). There was no difference in serum 25-OHVD levels between the subjects with a history of co-morbidities or those without and in the osteoporosis group or non-osteoporosis group (P>0.05). Cox's regression analysis was performed to evaluate the relationship between death and each of the baseline parameters with adjustment for age. 25-OHVD, presences of cardio-

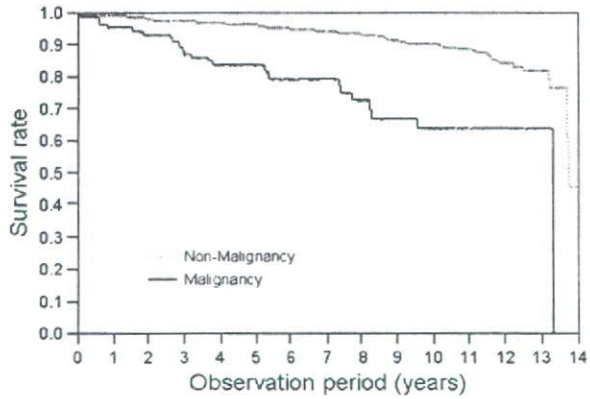

Fig. 2. Kaplan–Meier plots of survival by the presence or absence of malignancy. The prevalence of malignancy in baseline is associated with a significantly lower survival rate (log-rank test; P<0.01).

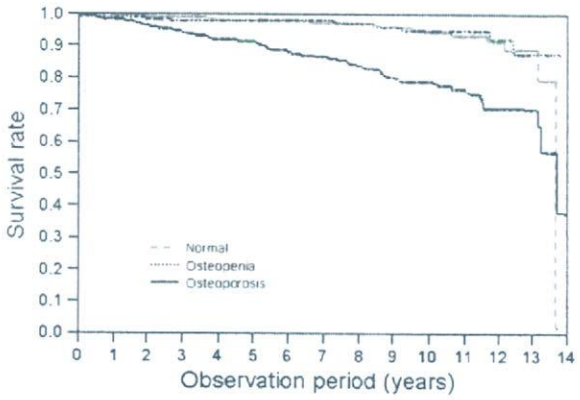

Fig. 3. Kaplan–Meier plots of survival by BMD category. Osteoporosis is diagnosed in accordance with the criteria of the Japanese Society for Bone and Mineral Research. Those with osteoporosis are associated with a significantly lower survival rate (log-rank test; $P<0.01$).

and cerebrovascular events, dementia, malignancy, smoking, drinking and prevalent fractures, and BMD, all indicated a significant correlation with death ($P<0.05$; Table 2). Multiple regression analysis was performed to evaluate the relationship between mortality and selected baseline parameters by the backward selection method (Table 3). Age, 25-OHVD, presence of malignancy and BMD at baseline were associated with mortality. The subjects who were treated with 1-alpha-OHVD3 for their osteoporosis during the observation period, were subtracted from the study in order to determine whether the hazard ratio of 25-OHVD for mortality was changed or not. However, the hazard ratio of 25-OHVD for mortality did not change when it was compared with before the subtraction of the subjects and after. Kaplan–Meier plots indicate a significant deference in survival rate when stratified by 25-OHVD (Fig. 1), presence of malignancy (Fig. 2) or stratified by BMD (Fig. 3). Serum 25-OHVD level <50 nmol/l, presence of malignancy or the presence of osteoporosis was shown to be associated with a significantly higher mortality rate (log-lank test; $P<0.01$).

Discussion

It has been well documented that the fractures are associated with increased mortality, especially 1 year after hip fractures [11,12]. However, little information has been available regarding the significance of baseline BMD on subsequent death in Asian population. The primary aim of the present study was to clarify whether Japanese postmenopausal women with osteoporosis are associated with a higher mortality rate than those without. The Cox hazard model demonstrated in the present study that osteoporosis is associated with a higher mortality rate than those without after adjustment for confounding factors. Therefore, we can conclude that osteoporosis not only in Caucasians but also in Asians may be associated with higher mortality than those without osteoporosis. However, the number of deaths was not sufficient to account for the difference in the cause of death between those with osteoporosis and the control subjects. The prevalence of low BMD is an important component of the risk for fracture. There are many reports that indicate the relationship between incident fractures and mortality in osteoporosis [5–14]. Therefore, fracture is thought to be a good predictor of mortality in subjects with low BMD. However, we should predict the mortality before fracture event. To clarify an early predictor of mortality, we investigated whether or not low BMD represented a risk factor for mortality in an ambulatory sample of Japanese patients. The study results demonstrate that low BMD is a significant independent risk factor for future death. However, in the present study, our model did not include prevalent fractures to predict subsequent death. This may indicate that low BMD is a better predictor for death than prevalent fractures. The exact reason why prevalent fractures did not predict future death, is unknown. But the clinical significance of fracture effect on death is more important in incident fracture than prevalent fracture, because the present participants may consist of the survivors from fresh fracture, which may affect the survival. The participants with osteoporosis showed a lower baseline prevalence of diabetes and dyslipidemia as risk factors for death. Furthermore, the baseline prevalence of hypertension, vascular events and malignancy between the osteoporosis and non-osteoporosis groups was not significantly different. The higher prevalence of dementia found at baseline in the osteoporosis group compared to that in the non-osteoporosis group may have contributed to the higher mortality rate in the present study. Although pre-existing dementia was not a significant risk factor for future death, it might represent possible causes of low activity in daily life and result in low BMD. Therefore, it is necessary to investigate whether or not dementia accounts for low bone density or whether it may be associated with subsequent low bone density. The prevalence of malignancy was another independent significant risk for future death in the present study. This phenomenon is thought to be within our expectation because some of the prevalent malignancies may have relapses. The low level of 25-OHVD observed frequently in elderly people [35–37] was found to be another significant independent risk factor for future death. A recent report indicates that lower serum 25-OHVD levels are associated with a higher risk of nursing home admission or mortality rate [24], suggesting that a lower (<50 nmol/l) 25-OHVD level may be used as an indicator of frailty. The higher risk for death in people with low 25-OHVD levels may be explained by the risk of sarcopenia [38], falls and low physical performance [39]. Furthermore, low 25-OHVD levels are reported to be associated with autoimmune disease, cancer, cardiovascular disease or diabetes [37,40,41]. A meta-analysis consisted of 18 randomized controlled trials reported that the intake of ordinary doses of vitamin D supplements seems to be associated with mortality [42]. However, this report stated that the relationship between mortality and baseline level of vitamin D would be required the further clarification [42]. Thus, the result of the present study may have some contribution to the issue between vitamin D and survival in elderly people. However, the present study showed no significant association between low 25-OHVD and these morbid states.

Our study has some limitations. First, there was a possible sampling bias that could have led to the participants having more serious illness than the general population, because our study population consisted of those who sought medical consultation for various reasons. However, the prevalence of co-morbidities, which had a potentially causal relationship to mortality, seemed to be unrelated to the higher mortality in the osteoporosis group. Second, 213 subjects who were lost to follow-up were included for analysis in this study; therefore, the survival rate reported may not be completely accurate. However, we think that those lost to follow-up were possibly distributed equally between the survivors and dead, because the subjects with no co-morbidity may have been less motivated to visit the clinic and those with serious illness may have dropped out due to their loss of mobility. Third, the participants with osteoporosis used some type of drug for osteoporosis therapy; therefore, the association between the incident fractures and mortality was unclear. A recent study using zoledronic acid for secondary prevention of fractures indicated that the zoledronic acid-treated group after hip fracture was associated with lower mortality than the control subjects [43]. Therefore, the mortality rate in osteoporosis may have been underestimated in the present study because of the treatment given for osteoporosis. However, despite the treatment given, the mortality rate in the osteoporosis group was higher than in the control subjects, clearly indicating that those with osteoporosis had a higher mortality rate than those without. Finally, we only studied Japanese women living in a rural area so that to confirm our finding, further investigation in a large sample of people from entire Japan or metropolitan areas is required.

Although the present investigation had several limitations, this is the first to address the association between low BMD or serum 25-

OHVD levels and mortality in Japanese women. In summary, the study findings suggest that the presence of osteoporosis and lower levels of 25-OHVD represent potentially powerful risk factors for mortality.

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ORIGINAL ARTICLE

Association between lumber bone mineral density and vascular stiffness as assessed by pulse wave velocity in postmenopausal women

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Abstract Recent studies have showed a significant correlation between vascular calcification and bone mineral density (BMD). Therefore, an investigation was carried out on the association between arterial stiffness, lumbar BMD and bone metabolic markers in Japanese postmenopausal women. Brachial-ankle PWV (baPWV) and BMD of the lumbar spine and serum bone-specific alkaline phosphatase (BAP) levels in 143 postmenopausal women were measured, where there was a significant negative correlation between baPWV and BMD ($r = -0.21$; $P = 0.0135$). An additional analysis included the remaining 75 subjects, but excluded subjects with hypertension and obesity. Here, a more negative correlation between baPWV and BMD ($r = -0.315$; $P = 0.006$), and a positive correlation between baPWV and BAP ($r = 0.248$; $P = 0.032$) were also significant. A group analysis, where the women were age matched and stratified into three groups of different bone density, i.e., normal BMD, osteopenic and osteoporotic, were further made. This showed lower PWV values in the normal BMD group than in the other two groups. A study also showed that the tertile with the highest BAP was associated with significantly higher PWV values than the other tertiles. However, when the multiple linear regression analysis was carried out, there was no correlation between PWV and BAP values. Low BMD and arterial stiffness show some correlation, suggesting that BAP may reflect the degree of arterial stiffness present.

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Keywords Bone mineral density · Brachial-ankle PWV · Bone-specific alkaline phosphatase · Arteriosclerosis · Osteoporosis

Introduction

Arteriosclerosis progresses with age, and the risk of arteriosclerosis in women increases significantly after menopause [1, 2]. On the other hand, bone mass decreases with age regardless of sex. However, women are at higher risk especially after menopause, when bone mass decreases rapidly due to a decrease in estrogen [3, 4]. It was recently shown that the degree of vascular calcification is significantly correlated with changes in bone density, suggesting that vascular sclerosis and decreased bone mass are closely linked pathological conditions [5–8].

Pulse wave velocity (PWV) can be used to measure the elasticity of arteries, thus providing an easy measure of progression of arteriosclerosis. Indeed, despite the fact that PWV values do not directly describe calcification of blood vessels, PWV is used as an effective measure of arteriosclerosis. Carotid-femoral PWV (cfPWV) has been a traditional method used to measure PWV. However, this method requires some technical skills. On the other hand, brachial-ankle PWV (baPWV), now available as a more convenient method, only requires placing blood pressure cuffs on the extremities. It has been reported that baPWV and cfPWV values are extremely well correlated within the same patient, suggesting that baPWV is as equally reliable as cfPWV as an index for the severity of arteriosclerosis as well as a prognostic indicator in the care of patients with hypertension [9, 10].

The most important objective of osteoporosis treatment lies in the prevention of bone fractures, which occur as

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

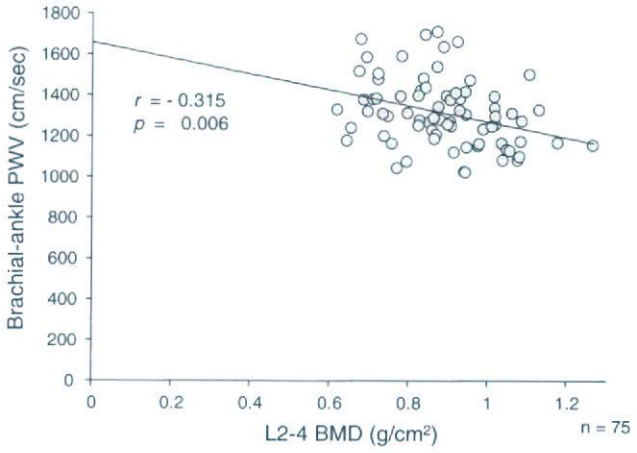

Fig. 1 An even stronger correlation was observed between L2–L4 BMD and PWV values after those with hypertension, a determining factor of PWV, and those with obesity as assessed by BMI, a determining factor of L2–L4 BMD, were excluded ($r = -0.315$; $P = 0.006$)

($r = -0.315$; $P = 0.006$) 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

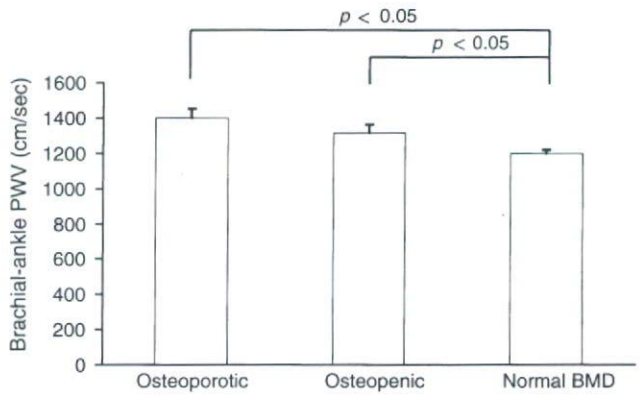

Fig. 2 The subjects in the normal BMD group showed significantly lower PWV values than the other two groups (1,201.1 ± 18.3 vs. 1,312.6 ± 49.0 cm/s, 1,201.1 ± 18.3 vs. 1,399.5 ± 54.1 cm/s; $P < 0.05$). All results are presented as mean ± SD. In these subjects, a significant negative correlation was shown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

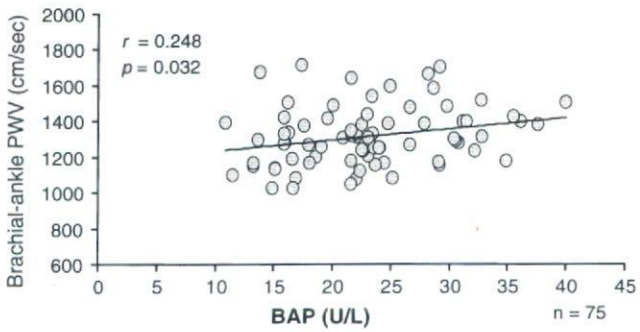

Fig. 3 PWV values showed a stronger positive correlation with BAP, a bone formation marker, in 75 subjects with normal blood pressure and BMI ($r = 0.248$; $P = 0.032$)

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

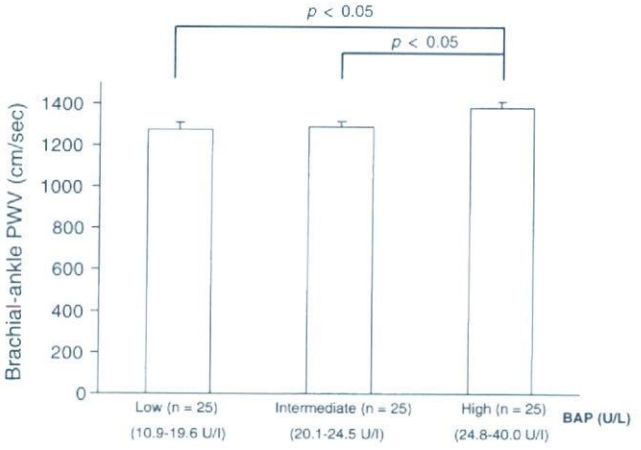

Fig. 4 The tertile with the highest BAP showed significantly higher PWV values than the other tertiles (1,308.8 ± 35.0 vs. 1,285.5 ± 27.6 cm/s, 1,308.8 ± 35.0 vs. 1,247.9 ± 35.6 cm/s; $P < 0.05$)

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.

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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
ーメタボリックシンドロームを中心にー

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

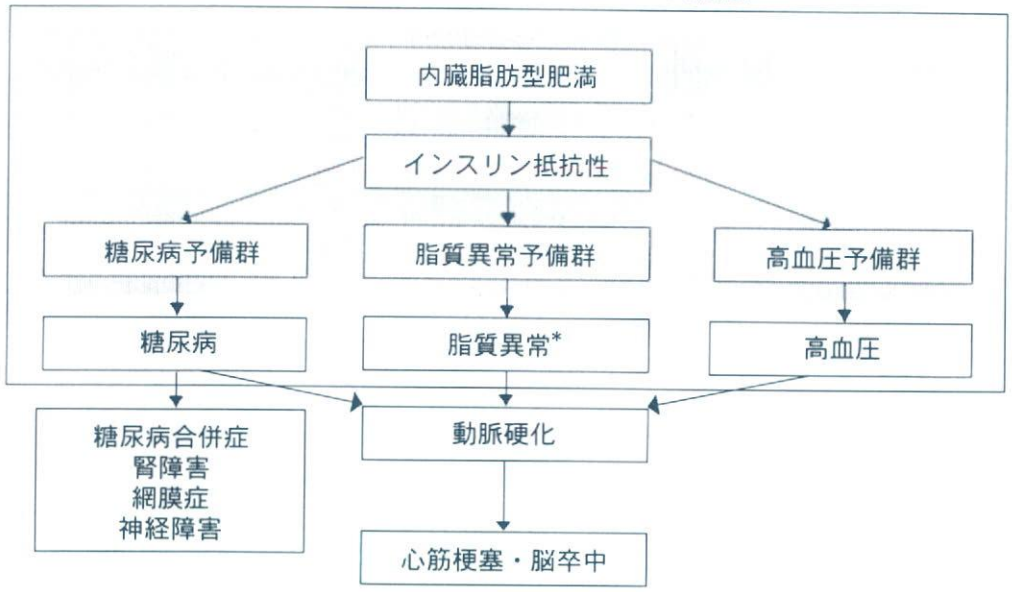
*日本動脈硬化学会、日本糖尿病学会、日本高血圧学会、日本肥満学会
日本循環器学会、日本腎臓学会、日本血栓止血学会、日本内科学会

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

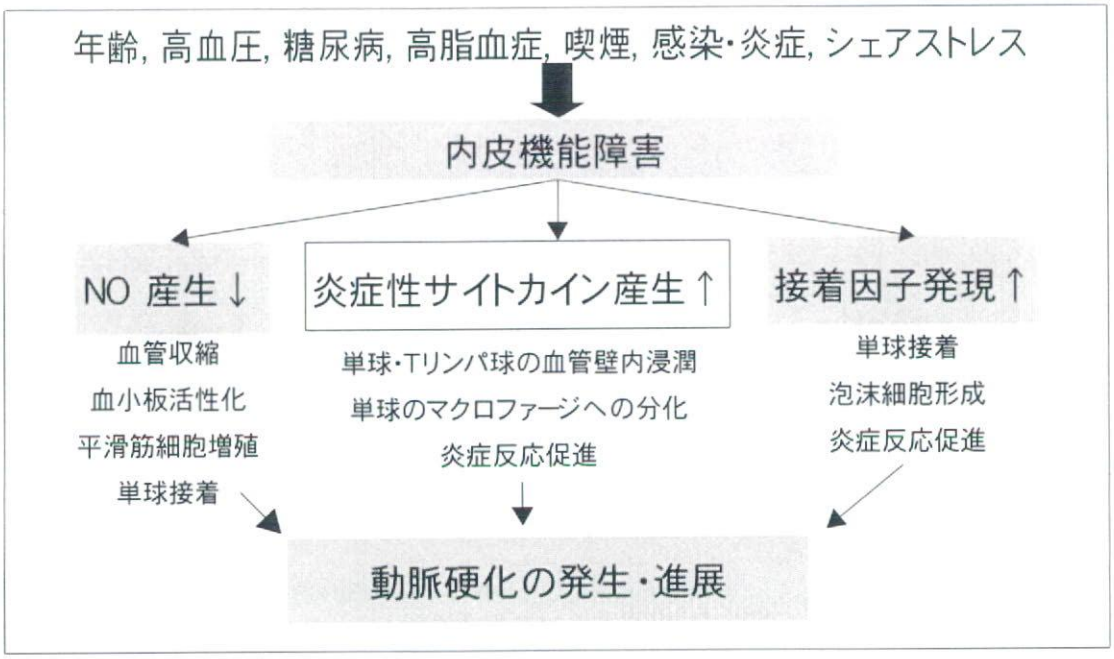


図2

動脈硬化の進展とその評価法

松尾　汎　Mebio 2005 改変

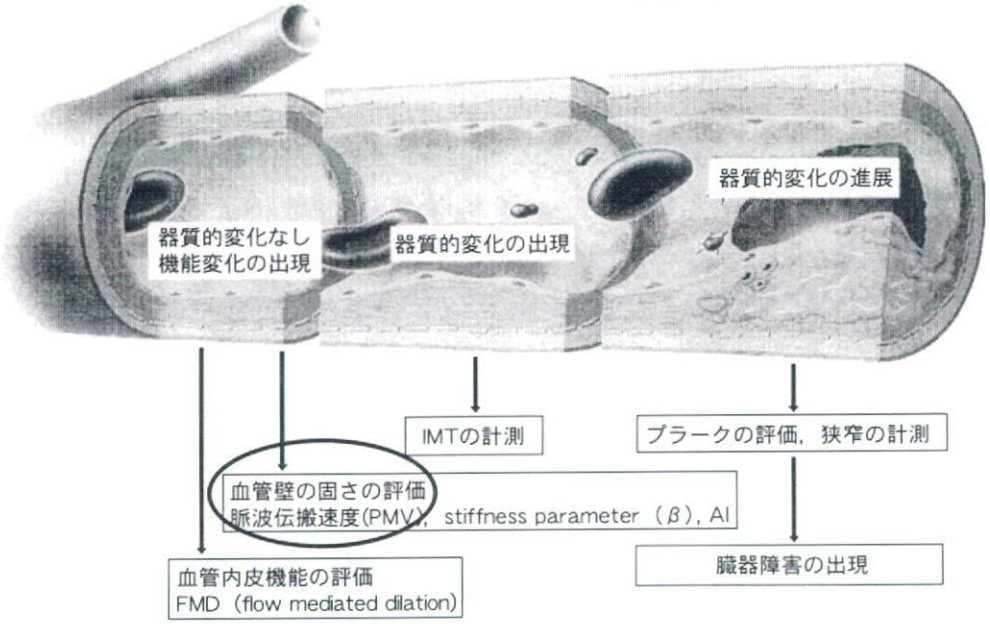


図3

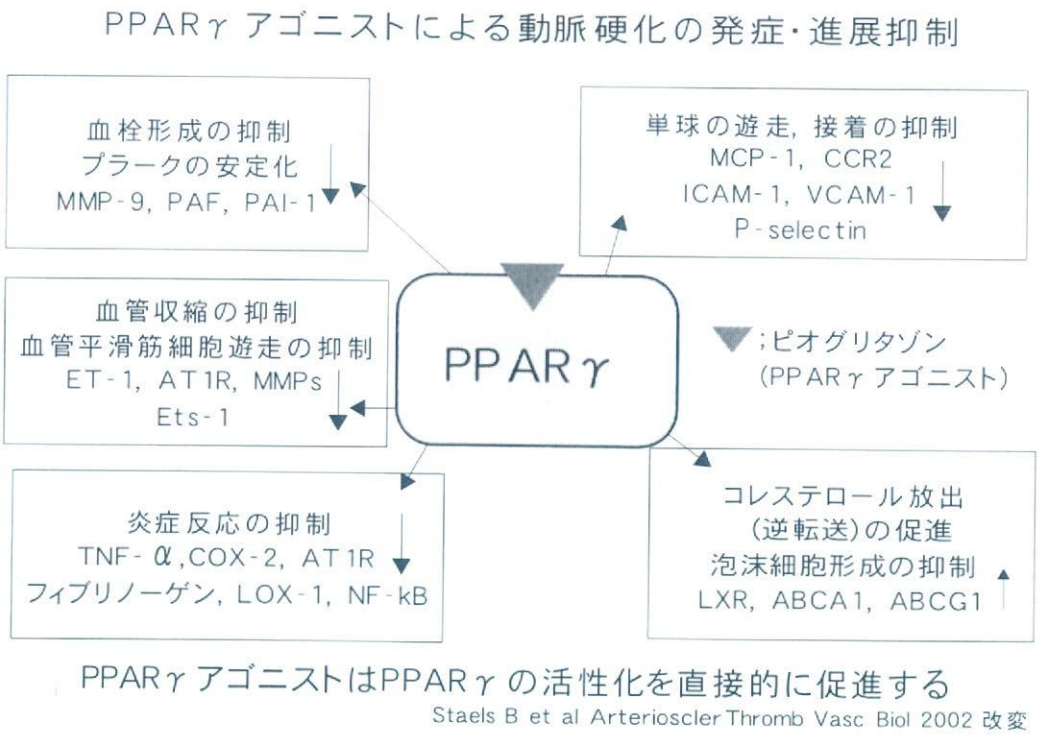


図4

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