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 (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 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 K, 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 also been reported not only in cross-sectional but in longitudinal studies [6,11] which 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 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, by 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. There is mounting evidence that suggest 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 assist 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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Legends for the figures

Figure 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)

Figure 2: The subjects in the normal BMD group showed significantly lower PWV values than the other two groups (1201.1 ± 18.3 cm/sec versus 1312.6 ± 49.0 cm/sec, 1201.1 ± 18.3 cm/sec versus 1399.5 ± 54.1 cm/sec; $P < 0.05$). 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.

Figure 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).

Figure 4: The tertile with the highest BAP showed significantly higher PWV values than the other tertiles (1308.8 ± 35.0 cm/sec versus 1285.5 ± 27.6 cm/sec, 1308.8 ± 35.0 cm/sec versus 1247.9 ± 35.6 cm/sec; $P < 0.05$).

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/sec)	1450 ± 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

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

Table 3. Background factors in the 3 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

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

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（循環器疾患等生活習慣病対策総合研究事業）

分担研究報告書

大規模成人女性を対象とした研究

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研究要旨

大規模女性コホート研究のデータを利用して，①メタボリックシンドローム（以下 Met-s）の横断的な有病状況検討および②曝露情報としての食事摂取状況及び身体活動状況の妥当性検討を実施し、以下の結果を得た。

① ウエスト周囲長が 80cm 以上の者の割合は 10.2%であり、国民健康・栄養調査結果よりは低かった。高血圧者（収縮機血圧 130mmHg 以上または拡張期血圧 85mmHg 以上）の割合は 22.6%であった。空腹時血糖値が 100mg/dl 以上の者の割合は 16.0%であった。高コレステロール・低 HDL コレステロールを示す者の割合は 34.7%であった。Met-s を示す者の割合は 3.4%と低かった。いずれの項目についても、高齢になるにしたがい、その割合が高くなっていた。

② 妥当性検討に応じた 42 名を対象として、連続 1 週間の食事日誌（記録法）および食品摂取頻度調査票による調査を、季節変動を考慮するため、8～9 月と翌年の 2～3 月の 2 回、同一対象者に対して実施した。身体活動量に関しては、加速時計（ライフコーダーEX：スズケン）を用いて、連続 1 週間の日常身体活動量を測定した。本検討では、調査が終了したばかりで、現在データの入力・整理を行っており、来年度の早い時期に解析を実施する予定である。

A．研究目的

わが国で女性の健康に関心が持たれ始めたのは 2000 年以後であり、大病院での女性専門外来の設置という形で具体化され、2004 年 3 月には性差医療・医学研究会が発足した。このように、高齢社会における女性特有の生活習慣・保健習慣に焦点を当てた健康増進対策が必要とされている。

喫煙・飲酒・栄養・運動などの日常生活習慣や各種の保健習慣において、疾患予防の観点からのエビデンスが、大規模疫学研究によって提供されてきた。しかしながら、その多くは男女共通の要因探索が主であった。生活習慣は男女で大きく異なり、また標的となる疾患も異なるため、女性における生活習慣の健康影響についてのエビデンスは現在大きく不足している。日常の生活習慣にくわえて、経口避妊薬・更年期障害治療など外因性ホルモンへの長期曝露、痩身ダイエット、妊娠中もしくは閉経後のビタミン剤・栄養補助剤など、女性に特徴的な保健習慣による健康影響についても、わが国ではほとんど検討されていない。このような状況に対して、女性特有の健康問題を解明し、女性の生涯ステージに応じた健康ケアの疫学的エビデンスを確立することを目標として、全国の女性看護職を対象者とした大規模女性コホート研究である「日本ナースヘルス研究（JNHS）」を 2001 年末に開始した。

本研究では、この大規模女性コホート研究のデータを利用して，メタボリックシンドローム（以下 Met-s）の有病状況・死亡や生活習慣について、(1)Met-s を含めた生活習慣病の有病状況およびそれに関連した死亡の把握及びその妥当性の検討、(2)サブ

サンプルを対象とした，食事調査票および身体活動調査項目の妥当性検討、(3)生活習慣病の実態(1)と生活習慣の実態(2)との関連の，大規模女性研究データを利用した検討を行うことを目的としている。

本年度は、(1)に関して、Met-s の有病状況の横断的検討を、(2)に関して食事摂取状況および身体活動の妥当性検討を実施している。

B．研究方法

(1) Met-s の有病状況の横断的検討

大規模女性看護職コホート研究の自記式ベースライン調査票（2001-2004 年）のデータを用いた。本コホートの対象者は 30 歳以上の女性看護職 42560 名であり、そのうち、身長、体重、ウエスト周囲長、血圧値（収縮期、拡張期）、血中脂質値（血清総コレステロール、血清 HDL コレステロール）、空腹時血糖値の情報があり、人工閉経者以外の 40～59 歳の 9,647 名を解析対象とした（図１）。なお、Met-s の診断基準は、本対象者においてはウエスト周囲長が 90cm 以上の者は 2%にしかすぎないことから、International Diabetes Federation (IDF)の定義を用いた。さらにここでは、中性脂肪の測定がないことから、高脂血症の判定を総コレステロール（220mg/dl）と HDL コレステロールの組合せで行った（図２）。

(2) 食事摂取状況および身体活動の妥当性検討

大規模女性看護職コホート研究のサブサンプル 80 名に対して、妥当性検討への参加を呼びかけ、それに応じた 42 名を対象とした。食事調査の標準法として、連続１週間の食事日誌（記録法）および食品摂取頻度調査票による調査を、季節変動を考慮するため、８～９月と翌年の２～３月の２回、同一対象者に対して実施した。身体活動量に関しては、加速時計（ライフコーダーEX：スズケン）を用いて、連続１週間の日常身体活動量を測定した。

C．研究結果

(1) Met-s の有病状況

ウエスト周囲長が 80cm 以上の者の割合は全体では 10.2%であり、国民健康・栄養調査結果よりは低かった。年齢階級別には、40～44 歳；7.2%、45～49 歳；10.8%、50～54 歳；12.1%、55～59 歳；15.7%となっており、高齢になるに従いその割合は上昇していた（図３、表１）。

高血圧者（収縮機血圧 130mmHg 以上または拡張期血圧 85mmHg 以上）の割合は全体では 22.6%であった。年齢階級別には、40～44 歳；12.3%、45～49 歳；61.8%、50～54 歳；34.2%、55～59 歳；43.0%であり、本対象については 40 歳代後半における高血圧者割合が最も高かった（図４、表１）。

空腹時血糖値が 100mg/dl 以上の者の割合は全体では 16.0%であった。年齢階級別には、40～44 歳；11.5%、45～49 歳；15.1%、50～54 歳；21.1%、55～59 歳；24.9%となっており、高齢になるに従いその割合は上昇していた（図５、表１）。

高コレステロール・低 HDL コレステロールを示す者の割合は全体では 34.7%であった。年齢階級別には、40～44 歳；25.4%、45～49 歳；31.8%、50～54 歳；45.7%、55～59 歳；54.4%となっており、高齢になるに従いその割合は上昇していた（図６、表１）。

Met-s を示す者の割合全体では 3.4%と低かった。年齢階級別には、40～44 歳；

1.7%、45～49歳;2.9%、50～54歳;4.8%、55～59歳；7.4%となっており、高齢になるに従いその割合は上昇していた（図7、表1）。

(2) 食事摂取状況および身体活動の妥当性検討

本検討における調査が、先日終了したばかりであり、現在そのデータを入力し、栄養素摂取量や身体活動量を算出する準備を行っている。本データの解析は来年度の早い時期に実施する予定である。

D．考察および結果

喫煙・飲酒・栄養・運動などの日常生活習慣において，疾患予防の観点からのエビデンスが，大規模疫学研究によって提供されてきた。しかし，その多くは男女共通の要因探索が主であった。生活習慣は男女で大きく異なり，女性における生活習慣の健康影響についてのエビデンスは現在大きく不足している。そこで，全国の成人女性を対象とした大規模研究の実施は，女性特有の健康問題を解明し，女性の生涯ステージに応じた健康ケアの疫学的エビデンスを蓄積する上で重要である。

本研究では調査票による自己申告により、生活習慣の調査を行っている。しかし、質の高い研究であるためには、曝露情報としての生活習慣についての正確な情報の把握が前提となる。そのため、自己申告による生活習慣情報が正確であるかどうかを確認する妥当性検討を行っており、それらの結果を踏まえて、今後生活習慣と疾病発生状況の関連を横断的及び縦断的に検討することとしている。

E．研究発表

学会発表

1．宮崎有紀子，林邦彦，小林亜由美，松村康弘，水沼英樹，今関節子，鈴木庄亮：女性看護職の生活習慣の再現性に関する検討．第66回日本公衆衛生学会総会，2007年10月24日，松山

o2000-2004年に実施した日本ナースヘルス研究ベースライン調査対象者：
30歳以上の看護職女性42,560名

↓

o上記対象者の内、以下の情報があり、人工閉経者を除いた40～59歳の9,647名（40～44歳，3,499名；45～49歳，3,048名；50～54歳，2,252名；55～59歳，948名）
・身長、体重、ウエスト周囲長
・血圧値（収縮期血圧、拡張期血圧）
・血清総コレステロール値、血清HDLコレステロール値、空腹時血糖値

図1　対象者の選出

腹腔内脂肪蓄積		
ウエスト周径囲 ≧ 80cm		
上記に加え以下のうち2項目以上		
高Cho血症	かつ／または	≧220mg/dL
低HDL-C血症		＜40mg/dL
収縮期血圧	かつ／または	≧130mmHg
拡張期血圧		≧85mmHg
空腹時高血糖		≧110mg/dL

図2　本研究におけるMet-sの診断基準

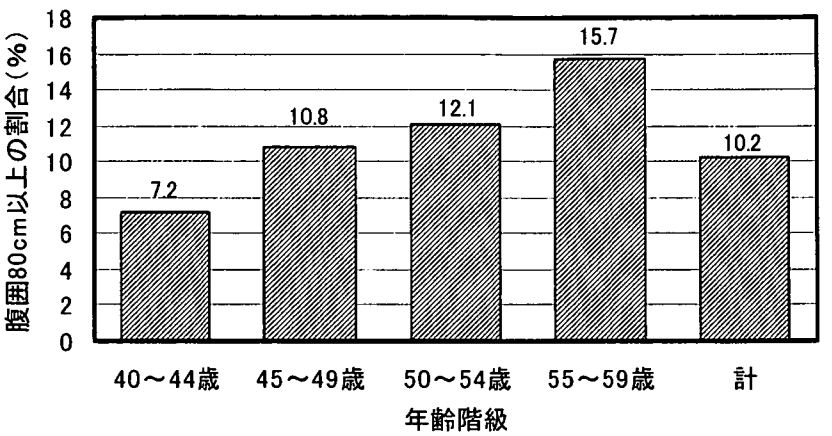

図3　年齢階級別の腹囲80cm以上者割合

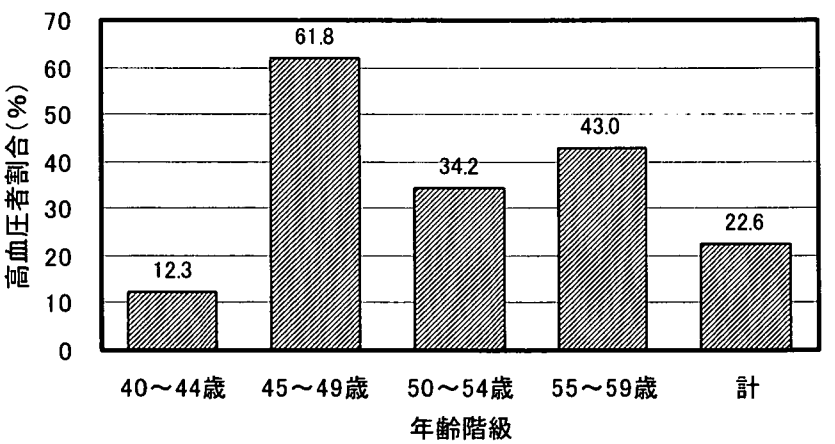

図4　年齢階級別の高血圧者割合