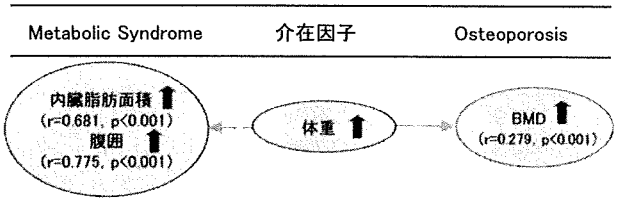
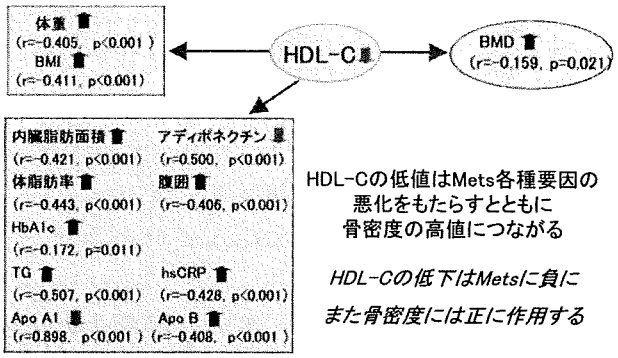


体重があると内臓脂肪面積と腹囲の増大とともに
骨密度の高値につながる

体重はMetsに負に，また骨密度には正に作用する

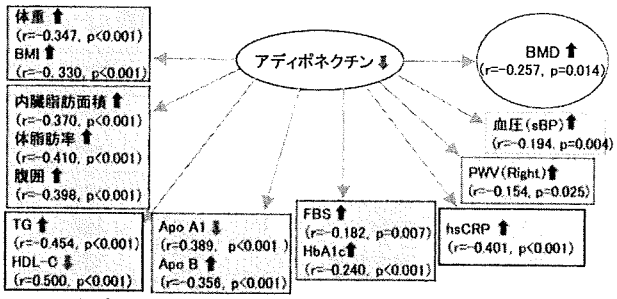
【図11】メタボリックシンドロームと骨粗鬆症との疾患関連性(1)



HDL-Cの低値はMets各種要因の
悪化をもたらすとともに
骨密度の高値につながる

HDL-Cの低下はMetsに負に
また骨密度には正に作用する

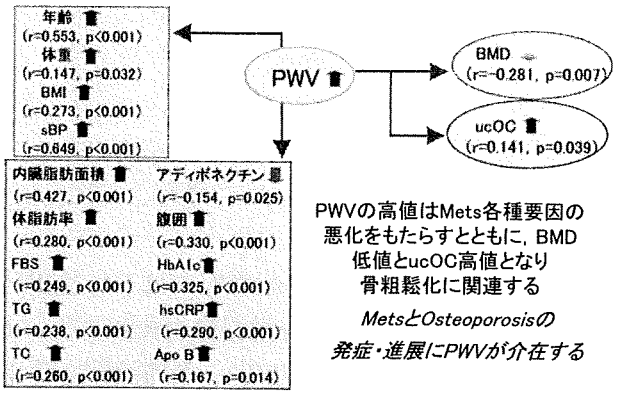
【図12】メタボリックシンドロームと骨粗鬆症との疾患関連性(2)



アディポネクチンの低値は内臓脂肪，脂質異常，糖代謝異常，炎症マーカーの高値および血圧の上昇や動脈硬化に関係し，BMD高値となる

アディポネクチンの低値は臓器脂肪の増加，脂質・糖代謝異常，血圧・動脈硬化などMetsに負に，また骨密度には正に作用する

【図13】メタボリックシンドロームと骨粗鬆症との疾患関連性(3)



PWVの高値はMets各種要因の
悪化をもたらすとともに，BMD
低値とucOC高値となり
骨粗鬆化に関連する

MetsとOsteoporosisの
発症・進展にPWVが介在する

【図14】メタボリックシンドロームと骨粗鬆症との疾患関連性(4)

する[48)49)]ことで，骨量が増加すると考えられる．

一方で，過体重，すなわち肥満では一般に脂肪量が増加することから，脂肪の増加こそが肥満における骨量増加の誘因であると推察されてきた．他方，脂肪組織を構成する白色および褐色脂肪細胞は，骨芽細胞や軟骨細胞・筋芽細胞と同様に中胚葉由来の細胞を起源とする．実際に，老年期の骨粗鬆症において骨髄中の脂肪細胞が増加し，骨芽細胞が減少する[50)]こと，幼年期における骨折は肥満のリスクを高めること[51)]などからも脂肪細胞と骨代謝との関連性が示されている．そのため，これらの細胞分化方向を制御する分子機構の解明が，Metsの治療法における鍵の1つであると考えられる．

近年，脂肪細胞や骨芽細胞分化を制御する因子群が多数報告されているが，興味深いことにこれらの因子は相互の分化を制御する例が多い．特に脂肪細胞分化促進因子である核内レセプター型転写因子PPAR-γは同時に骨芽細胞分化抑制機能を有することが知られ，骨代謝におけるPPAR-γ機能の重要性が示唆されている．すなわち，本来脂肪細胞分化制御因子として報告されたPPAR-γであるが，骨髄間葉系幹細胞においてもPPAR-γリガンド(チアゾリジン誘導体)が脂肪細胞を促進[52)]し，骨芽細胞分化を抑制することから，PPAR-γが前駆脂肪細胞から脂肪細胞のみならず，間葉系幹細胞からの分化の方向性を規定する因子であることが見出されている．

また，PPAR-γ欠損ヘテロマウスの解析からもPPAR-γが骨量を負に調節する[53)]ことが支持されているが，近年破骨細胞特異的PPAR-γKOマウスの結果から，PPAR-γがC-FOSを標的遺伝子として破骨細胞分化誘導に機能することが示唆された[54)]ため，骨代謝全体におけるPPAR-γの作用点は骨芽細胞と破骨細胞のどちらが重要であるかは

今後の課題となっている.

これらのことから，過体重すなわち肥満による脂肪細胞の活性化はPPAR-γによってなされるが，一方でPPAR-γは骨代謝に抑制的に作用するため，骨密度に負に傾く．今回の本研究結果とは逆のことが想定される．このことは2型糖尿病における骨量増加および骨折増加から説明できるかもしれない[55)-57)]とされている．すなわち，過体重から骨密度は増加するが，PPAR-γによって骨代謝が抑制されるので，骨質の劣化につながり，易骨折性を呈する可能性がある．従って過体重であって，インスリン欠乏状態，高血糖状態，それに糖尿病に伴う合併症がある．さらに絶対的・相対的インスリン欠乏が骨芽細胞の機能や数を低下させ，持続は高血糖により骨芽細胞機能のさらなる低下が招来され，骨折の危険性がより高くなるものと思われる.

②HDL-Cの骨密度およびVFAに対する関与

脂肪組織蓄積に並行して出現する高TG血症，低HDL-C血症の骨に対する影響は現在のところ明らかではない．本研究ではTG高値は骨密度との相関はなく，HDL-C低値のみ骨密度との相関を認めている．またTG高値およびHDL-C低値はVFAと正の相関を予想通り認めている．HDL-C低値と骨密度高値との関係については，いくつかの報告があるが，現時点では意見の一致をみていない．すなわち，Hsu et al.[58)]は中国人を対象に7,137人の男性，4,585人の閉経前女性，2,248人の閉経後女性において，年齢，身長，% fat，身体活動性，喫煙，飲酒量等で補正後，男性，閉経前女性，閉経後女性いずれの群においてもTGは全身BMCに対して有意な負相関を示したが，HDL-Cは有意な相関を示さなかったという．さらに70歳以上の中国人男性368人を対象に，年齢，身長，体重，% fat等で補正後，TGは超音波で測定した踵骨骨密度とは正の相関を示し，HDL-Cは有意な相関を示さなかった[59)]．白人閉経後女性1,176人を対象としたBagger et al.の報告[41)]では，年齢，閉経後年数，BMI，% fat，喫煙，身体活動性等で補正後，TGとHDL-Cのいずれも大腿骨頸部および腰椎骨密度と有意な相関を示さなかった．しかし，椎体骨折群では非骨折群に比較して有意にTGが低値であったという.

一方，日本人閉経後女性214人を対象とした研究[60)]では，年齢，閉経後年数，BMI，% fatで補正後，TGは腰椎，大腿骨頸部，橈骨のいずれの骨密度とも有意な相関がなかったが，HDL-Cは腰椎および橈骨の骨密度と有意な正相関を示し，本研究結果と一致していた．さらにYamaguchi et al.[60)]はBagger et al.[41)]と同様に，椎体骨折群では非骨折群に比較して有意にTGが低値であり，ロジスティック解析ではTGが1SD上昇するごとに，椎体骨折の危険率は0.51倍と有意に低下したという．またノルウェーの白人男女27,159人を対象としたAhmed et al.[61)]は，肥満，高TG血症，低HDL-C血症，高血圧のMetsの各因子が192人に重複するほど非椎体骨折の相対危険率が低下し，3つ以上の重複では危険率が男性においては0.71倍，女性においては0.66倍低下したという.

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

③アディポネクチンの骨密度およびVFAに対する関与

次にアディポネクチンと骨密度およびVFAとの関係に関してまとめると以下のごとくなる．アディポネクチンの低値はVFAとウェスト周囲径の増大をもたらすと共に骨密度高値につながるが，VFAとウェスト周囲径の増大は過体重によって示される骨密度の増大に結びつくものと考えられる．アディポネクチンと骨密度との関連性を初めて報告したものはLenchik et al.[62)]であると思われる．この報告によると，年齢，性，人種，喫煙，糖尿病状態を補正後，血清アディポネクチンは部分的骨密度($r=-0.20$ to -0.30, all $p<0.01$)，容積測定の骨密度($r=-0.35$ to -0.44, all $p<0.01$)および内臓脂肪量($r=-0.30$, $p<0.01$)と負に相関したという．これらのデータはアディポネクチンが骨密度に対するVFAの保護効果を示している可能性があるという．しかし，一方でアディポネクチンは骨密度に何の効果も発揮しなかった

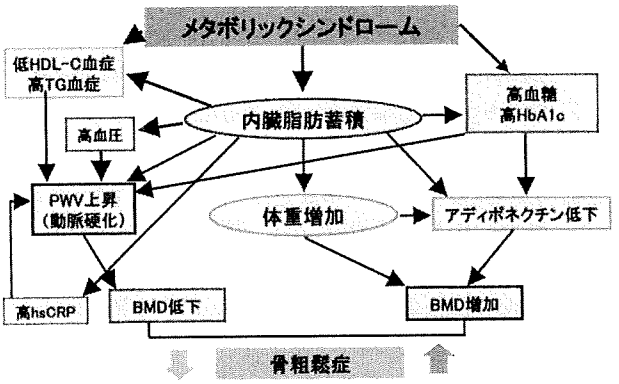
が，レプチンは負の効果を発揮するという報告[63]がある．しかし，Third US National Health and Nutrition Examination Surveyによる大規模研究[64]ではレプチンと骨密度との相関は明らかにすることはできなかったという．レプチンの骨代謝における役割は研究によって骨密度と正にも負にも相関することが示されており，明らかではない[65]．また，最近のJürimäe et al.の研究[66]によると閉経前女性におけるアディポネクチンは骨密度値の変位の3～12%を説明し，レプチンよりもアディポネクチンの方が骨代謝とより直接的に関係する重要なシグナルを与えている可能性があるとしている．このメカニズムとしてアディポネクチンがCOX-2を介して骨代謝効果[67]を及ぼすとされている．しかし，一方で血清アディポネクチンと骨密度とは負の関係にあり，これは閉経後女性に限ったことで，閉経前女性ではないという[65]．このことはエストロゲン補充療法を行っている閉経後女性が，行っていない閉経後女性よりも低いアディポネクチンレベルを有していることが認められ[68]，エストラジオールレベルがアディポネクチンレベルと負に相関することから示されている[69]．閉経後女性では脂肪組織がエストロゲンの主な源となり[70]，続いてBMIが低ければエストロゲンがより低く，アディポネクチンがより高くなる．またアディポネクチンはMAPKシグナル回路を介してRANKLを刺激し，OPGの発現を抑制し[71]，RANKLは骨吸収への強い刺激であり，OPGはRANKL誘導される骨損失を防ぐ[72]ことから，アディポネクチンは骨吸収のRANKL回路の促進を通して骨代謝に効果を発揮する[65]のではないかという．

肥満は心血管系疾患や糖尿病を含めた多数の疾患に対しては負の影響を及ぼすにも関わらず，骨粗鬆症に対しては保護している[47]ようにみえる．体重とBMIがあると，骨折率は有意に低くなるという複数の報告[73)~76)]がある．骨密度の最も強い保護指標の1つである体重[46)77)~80)]は閉経後の骨密度喪失と骨代謝に対して負の相関[48)81)~85)]を示す．体重はFat MassとLean Massに依存しており，Reid et al.[85]によってレビューされているごとく，多くの研究ではFat Massと骨密度との有意な正相関を示してきた．しかし，脂肪代謝は異なる貯蔵庫であるため，Fat Massの分布は均質ではない．従って骨密度と骨代謝が貯蔵庫に依存する影響の可能性があるが，過去には研究されていなかった．

④PWVの骨密度およびVFAに対する関与

脂肪組織によって主に分泌されるレプチンはFat Massと有意に相関する[86]ので，レプチンの骨格への影響がより注目されている．一方，別の脂肪特異的蛋白質であり，肥満とともに減少するアディポネクチンの骨量に対する役割については知られていない[87)~89)]．マウスにおけるアディポネクチン療法は，肝の糖新生と筋肉のTGの減少[90]となり，アディポネクチンが脂肪細胞から筋肉や肝までシグナルを運ぶということを示唆するLenechik[62]のデータは，アディポネクチンが骨密度およびVFATとの強い負の相関性を呈している．対照的にはレプチンは骨密度と関連しなかったが，SFATやVFATおよび全体脂肪量とは有意に関連したという．アディポネクチンがレプチンよりも骨密度と強い関連性を示したという事実は興味深い．つまり，アディポネクチンが脂肪組織から骨までシグナルを運ぶかもしれないということを示唆している．アディポネクチンの特性として骨代謝調節に関与するといわれている．すなわち，アディポネクチンは破骨細胞形成を調節する2つの蛋白質であるRANKLやOPGなどのTNFのfamilyと構造類似性を有する．またアディポネクチンは破骨細胞形成に関与する転写因子であるNF-kBを抑制する[91]とともに活性化[92]するなど骨に影響を与える可能性が存在する．組換え型のアディポネクチンはプレアディポネクチンに由来する骨髄中のadipogenesisを抑制する．このことはアディポネクチンは骨髄環境に影響を及ぼす[93]ということである．

PWVの骨密度およびVFAに対する関与についてはPWVは骨密度と有意な負相関，ucOCとは有意な正相関を呈する．またPWVの年齢，体格，血圧に対する因子はいずれも有意な正相関を呈する．さらにPWVの脂肪蓄積に対する関与に



【図15】メタボリックシンドロームと骨粗鬆症との疾患関連性のまとめ

ついてはPWVと脂肪蓄積に対する各指標は有意な正相関を呈する.糖代謝に対する関与としては,PWVは糖代謝の各指標と有意な正相関を呈する.またPWVの脂質代謝および炎症マーカーに対する関与として,PWVはTGおよびhsCRPと有意な正相関を呈する.以上から,PWVの高値はMets各種要因の悪化をもたらすとともに,骨密度低値とucOC高値となり,骨粗鬆症の発症・進展にPWVが介在することが示されたものと考えている.

結　論

Metsと骨粗鬆症との疾患関連性をまとめると図15のごとくとなる.すなわち,Metsも内臓脂肪の蓄積だけに留まっている間は,主に体重増加とアディポネクチンの低下により,骨密度の増加を呈し,骨粗鬆症は併発しない.

しかし,内臓脂肪の蓄積を放置しておくと,高血糖,高HbA1c,高TG血症,高CRPを呈するようになり,それらに伴って骨密度の低下を来す.すなわち,Metsの予備段階では骨密度は増加し,骨粗鬆症を併発しないが,Metsが進行して血管が硬化し,動脈硬化を来してくると骨密度は低下し,骨粗鬆化を呈するので,Metsと骨粗鬆症は併発することとなる.従って,Metsに至らない内臓脂肪の蓄積の段階で予防策を講じれば,脂質代謝異常・糖代謝異常や高血圧の防止が可能となり,動脈硬化も抑止できる.動脈硬化が抑止できれば骨粗鬆化も招かないこととなる.すなわち,健全老化のためには健康教育,予防教育などの介入によりMetsの初期段階における内臓脂肪の蓄積を持続させないことが重要となる.これらの教育によって心血管イベントや糖尿病合併症の併発および骨粗鬆症性骨折など複数の生活習慣病の防止が可能となる筈である.このようなことから,内臓脂肪を指標とするわが国における施策である特定健診は的を射ているものと思われる.なお,今後の課題として,内臓脂肪の蓄積がどの程度のものがどの位の期間持続することにより,不可逆的な動脈硬化が形成されるのかを把握する必要がある.この考え方は約20年のDiabetusに掲載された仮説,高血糖の記憶(hyperglycemic memmory or metohlic memory),すなわちmetabolic exposureが借金となるという考え方とほぼ同様ではないかと思われる.Metabolic exposureの程度と期間が把握できれば,健全老化対策は可能となる筈である.

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Synopsis

The metabolic syndrome (Mets) has become the focus of the government-designated health checkup and health guidance initiatives that are currently in place as part of a comprehensive countermeasure against lifestyle-related diseases in Japan. At the same time, femoral neck fracture has tended to increase in incidence year after year and has drawn renewed attention as another lifestyle-related disease of interest, which makes affected individuals bed-ridden thus requiring nursing care. While these two diseases have generated much speculation about their association, their association remains largely unclear.

We have recently shown through an examination of these two diseases that as long as the Mets has not progressed beyond visceral fat accumulation, it is associated with increases in bone mineral density due to increased body weight and decreased adiponectin secretion, however, as the Mets progresses beyond that and begins to present with vascular sclerosis and atherosclerosis, it is associated with decreased bone mineral density, so that the Mets begins to coexist with osteoporosis. These findings suggest that health education and preventive medicine measures aimed at arresting visceral fat accumulation in early stages of the Mets are likely to lead to atherosclerosis and osteoporosis being suppressed, thus confirming the rationale for regular health checkups in which visceral fat accumulation is being targeted for detection and treatment.

To prevent the pathological aging process requiring medical intervention and nursing care, appropriate measures need to be taken to protect against the Mets and osteoporosis, as well as to protect lipid, vascular and bone health. Given the current expectations for Obstetrics and Gynecology in promoting women's health for life, it is clear that the specialty will have not a small role to play in female medicine in the years to come, as it continues to address both aging and estrogen deficiency as they affect female patients.

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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.

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.

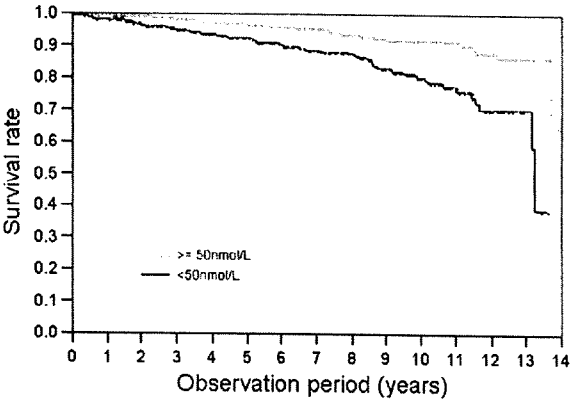

Fig. 1. Kaplan–Meier plots of survival by serum 25-hydroxyvitamin D level. 25-OHVD <50 nmol/l denotes deficiency and insufficiency; and ≥50 nmol/l, normal and borderline. There is a significant difference between the 25-OHVD categories (log-rank test; $P<0.01$).

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-

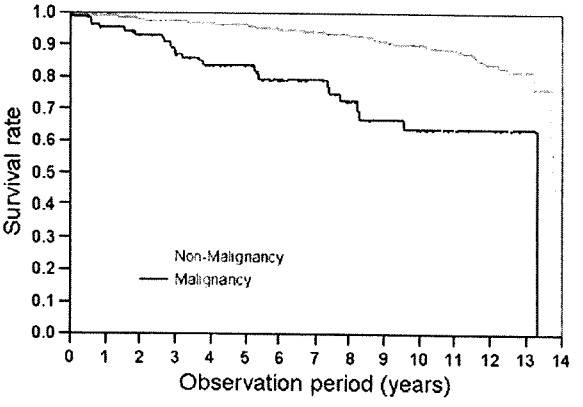

Fig. 2. Kaplan–Meier plots of survival by the presence or absence of malignancy. The prevalence of malignancy in baseline is associated with a significantly lower survival rate (log-rank test; $P<0.01$).

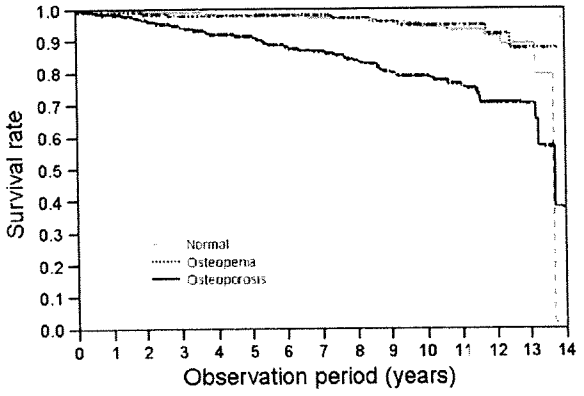

Fig. 3. Kaplan–Meier plots of survival by BMD category. Osteoporosis is diagnosed in accordance with the criteria of the Japanese Society for Bone and Mineral Research. Those with osteoporosis are associated with a significantly lower survival rate (log-rank test; $P<0.01$).

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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日本医師会生涯教育講座

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共催　東京都医師会
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テーマ「女性の健康支援としてのメタボリックシンドローム対策」

座　長　東京都医師会理事　相馬正義

1．産婦人科で果たす女性のメタボリックシンドローム対策

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1．はじめに

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

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

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

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

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

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

2．中高年ボランティア女性を対象とした最近の我々の研究から

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

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

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

表1　基本背景データ

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

平均的に見るとMetsでも動脈硬化でも骨粗鬆症でもない

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

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

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表2　血液検査データ

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

値内にて高値を示す集団ではなかった。

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

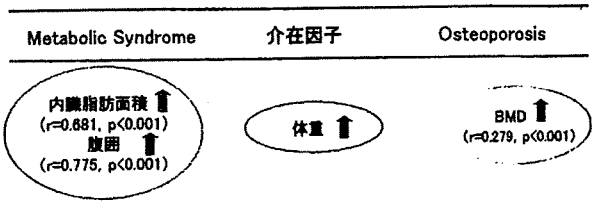
Mets診断基準項目であるウェスト周囲径90cm以上は33名（15.8％）、TG 150mg/dL以上は29名（13.1％）、HDL-C 40mg/dL未満は1名（0.5％）、FBS 110mg/dL以上は13名（5.9％）、血圧130/85mmHg以上は29％（13.1％）存在した。しかし、Metsの診断基準を充たすものは5名（2.3％）であった。また、原発性骨粗鬆症の診断基準により、骨粗鬆症は26名（11.9％）、骨量減少80名（39.3％）、正常107名（48.8％）であった。骨粗鬆症群および骨量減少群は正常群と比較し、低HDL-C、高ucOC、高PWVおよび低体重であった。一方、PWV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

表3　1日あたりの栄養摂取データ

		例数	Mean	SD	40-70歳代の平均値
摂取重量	(g)	182	2867.0	898.9	ND
摂取エネルギー	(kcal)	182	1805.2	465.3	1738
蛋白質	(g)	182	84.1	20.1	87.35
脂肪	(g)	182	54.3	20.9	48.4
炭水化物	(g)	182	249.4	63.9	251
Ca	(mg)	182	524.0	226.2	474.5
P	(mg)	182	1013.1	327.9	976.5
K	(mg)	182	2468.6	870.5	2488.5
n-3	(g)	182	2.5	1.02	ND
n-6	(g)	182	10.1	3.6	ND
Cholesterol	(mg)	182	265.0	144.0	294
VB1	(mg)	182	0.9	0.3	1.56
VB2	(mg)	182	1.3	0.4	1.47
VB6	(mg)	182	1.2	0.5	1.98
VB12	(μg)	182	7.8	5.1	7.1
葉酸	(μg)	182	339.2	135.1	332
VD	(μg)	182	8.7	4.7	8.28
VK	(μg)	182	307.4	171.5	256

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

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



体重があると内臓脂肪面積と腹囲の増大とともに骨密度の高値につながる

体重はMetsに負に，また骨密度には正に作用する

図1　メタボリックシンドロームと骨粗鬆症との疾患関連性(1)

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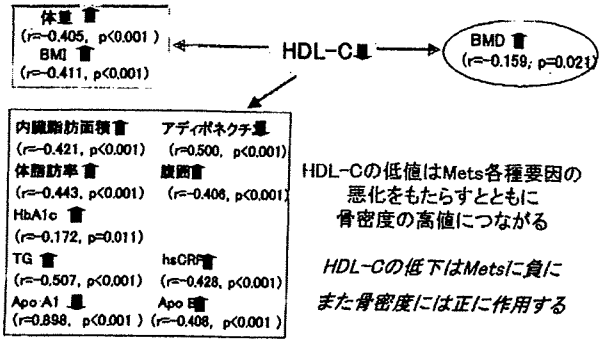

図2　メタボリックシンドロームと骨粗鬆症との疾患関連性(5)

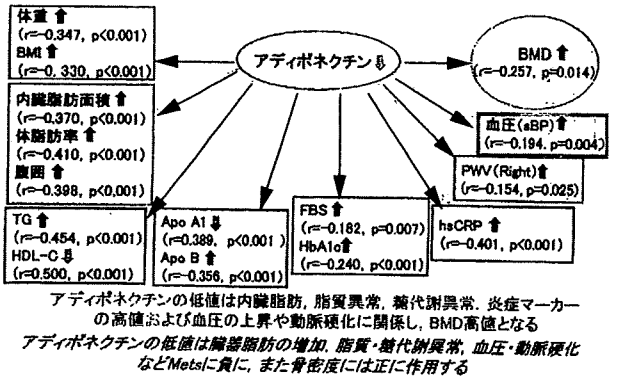

図3　メタボリックシンドロームと骨粗鬆症との疾患関連性(3)

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

(4)考察

①　体重の骨密度およびVFAに対する関与

BMDの維持には重力による負荷が必要であり、寝たきりは骨粗鬆症の発症を惹起する。逆に肥満では骨にかかる重力負荷が増大するため、骨量は増加すると考えられる。実際に高齢者を対象としたフラミンガム研究では、体重やBMIと高い相関を示すことが報告[8]されている。肥

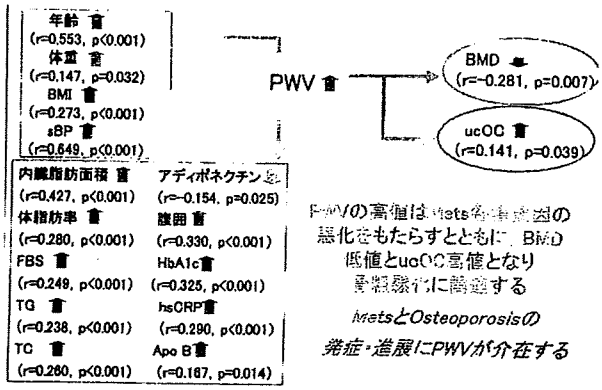

図4　メタボリックシンドロームと骨粗鬆症との疾患関連性(6)

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

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

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

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

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

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

② HDL-Cの骨密度およびVFAに対する関与

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

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