齢者でもっとも大きな低下率を示した.

5) BMIは男女とも初回調査時にすでに前期と後期高齢者に大きな差が存在していたが（図3），その後10年間の変動パターンはほぼ等しく，有意な変化を示していない.

6) 血清アルブミン値は，初回調査時（1992年）から1996年までは男女ともほぼ横ばいであるが，1996年から2002年にかけて男女ともまた前期・後期高齢者においても著明な上昇が認められた（図4）．この理由は，本研究の観察対象地域で，TMIG-LISA後半（1996年以降）に脳卒中予防も含めた食の改善運動が，地域一丸となって取り組まれ，動物性たんぱく質摂取の重要性について，あらゆる機会を通じて啓蒙普及活動が行われた結果と考えられている[8].

7) 血清総コレステロールについても男女で異なったパターンが認められた（図5）．男性は，1992年の初回調査時において前期高齢者で低く，加齢にともなって10年間で約8 mg/dlの低下が認められた．後期高齢者ではベースラインから高値が維持され，加齢にともなう低下がまったく認められなかった．一方，女性は前期・後期にまったく差がなく，ベースラインから最初の4年間では変化がなく，後半の6年間で有意に低下した.

図3　体格指数の変化

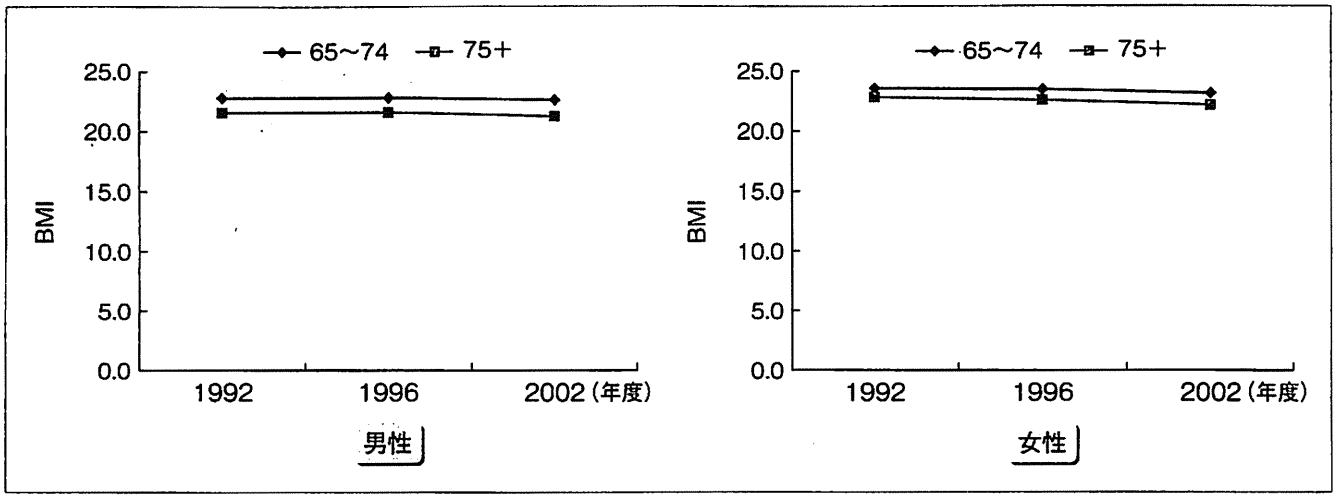


図4　血清アルブミン値の変化

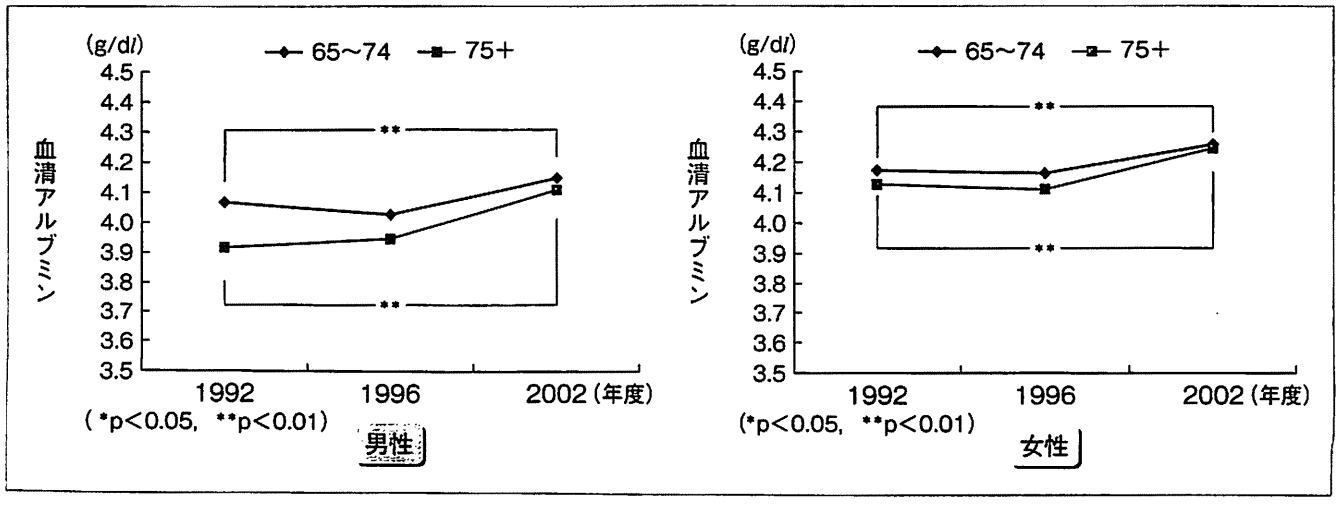
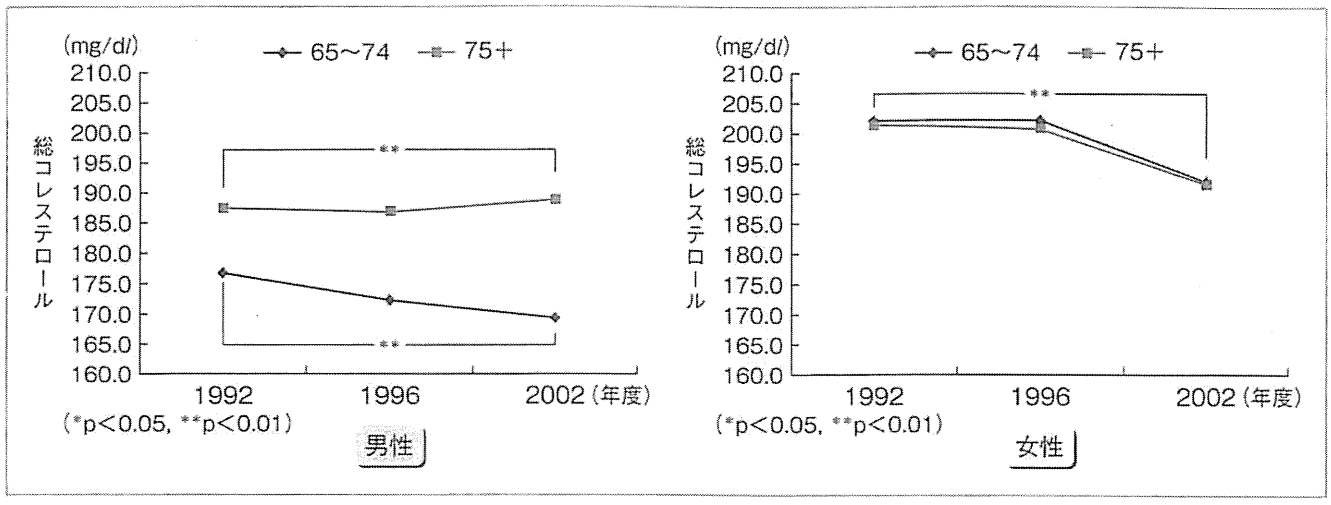


図5　総コレステロール値の変化



●1992年高齢者コホート（'92年群）と2002年高齢者コホート（'02年群）の各測定項目の比較

1）握力は，総じて'02年群で大きく，男性では65～69歳と80歳以上で有意に大きく，また女性ではすべての年齢階級で'92年群に比べて'02年群で有意に大きかった（図6）．

2）開眼片脚起立時間は，男女ともに'02年群で長時間起立が可能であり，とくに女性で80歳以上を除くすべての年齢階級において'02年群の起立時間が'92年群に比べて有意に長かった．

3）通常歩行速度は，男性，女性ともにすべての年齢階級で'02年群が有意に速かった（図7）．最大歩行速度についても，女性はすべての年齢階級で'02年群が有意に速かった．

4）BMIは，総じて'02年群で大きく，とくに男性で'02年群の65～69歳と70～74歳群で有意に大きかった．女性では75～79歳群のみ'02年群で有意に大きかった（図8）．

5）血清アルブミン値は，男女の全年齢階級で'02年群コホートが有意（$p<0.001$）に高かった（図9）．

6）血清総コレステロールは，女性では両群に有意差は認められなかったが，男性では80歳以上で'02年群が有意に高い値を示した

図6　握力の差異

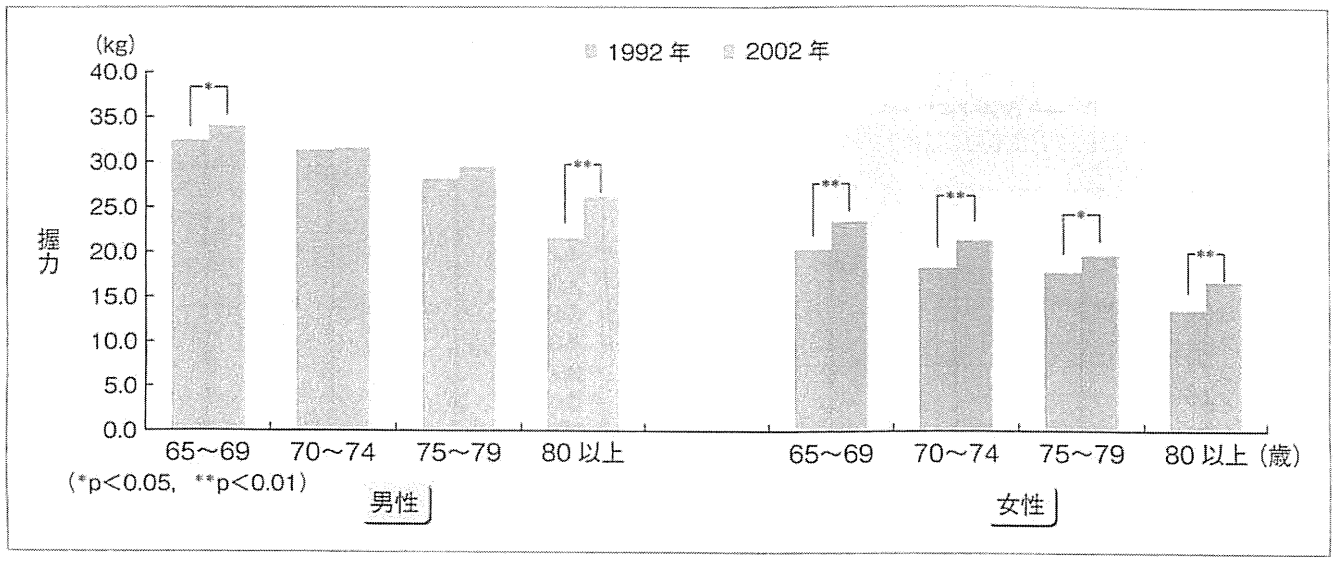


図7　通常歩行速度の差異

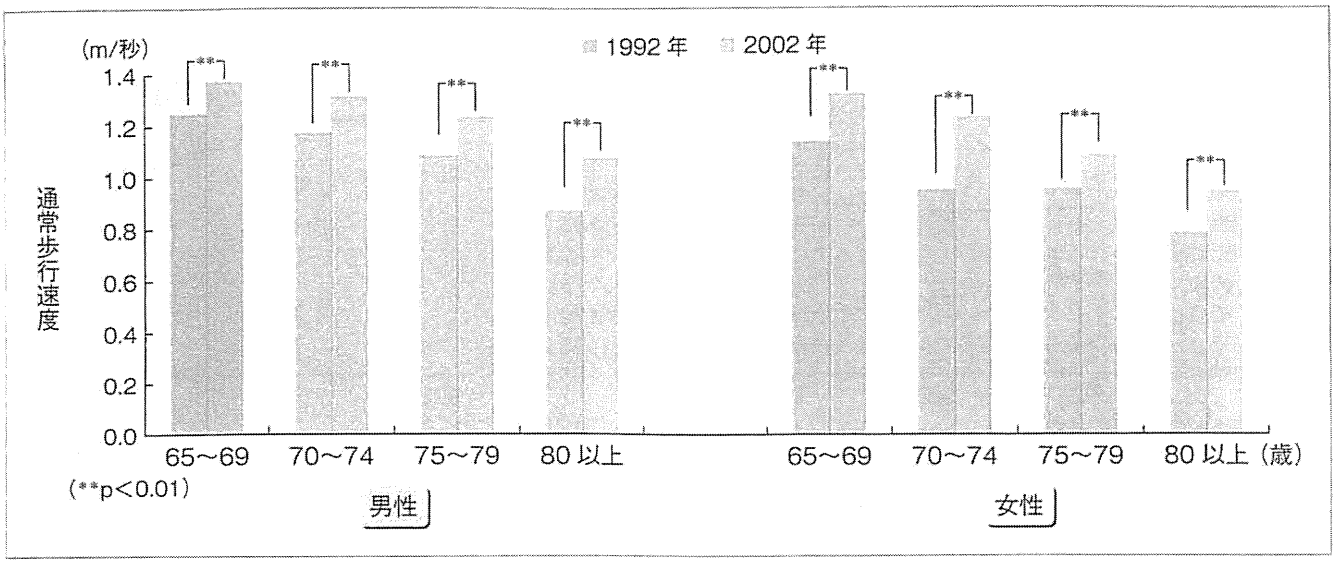


図8　体格指数の差異

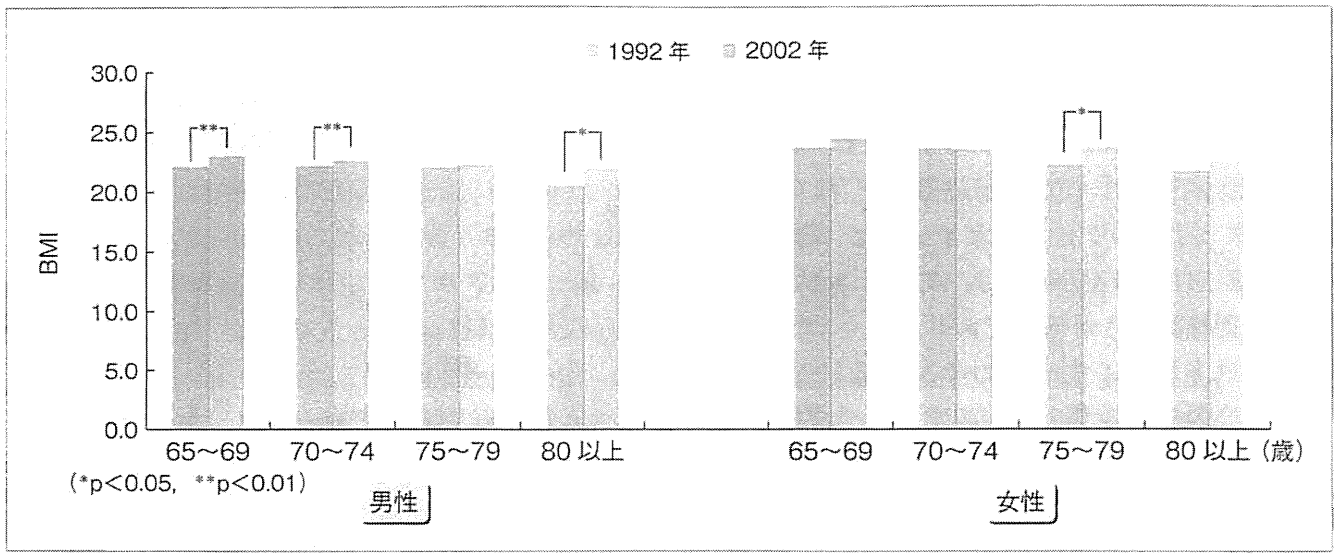


図9　血清アルブミン値の差異

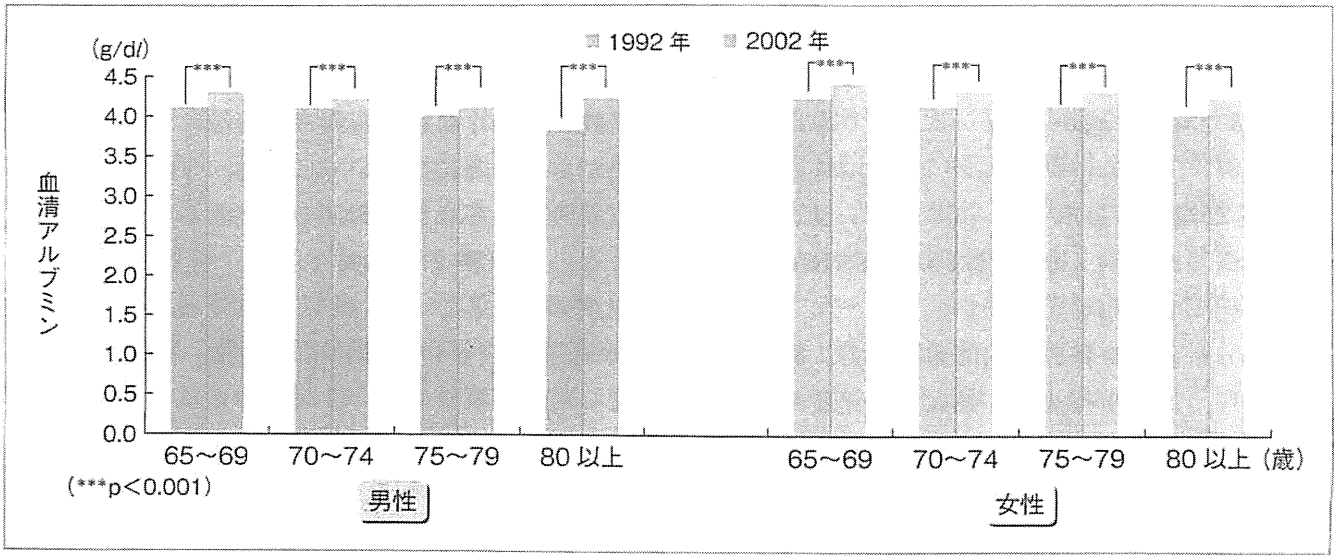


図 10　血清コレステロール値の差異

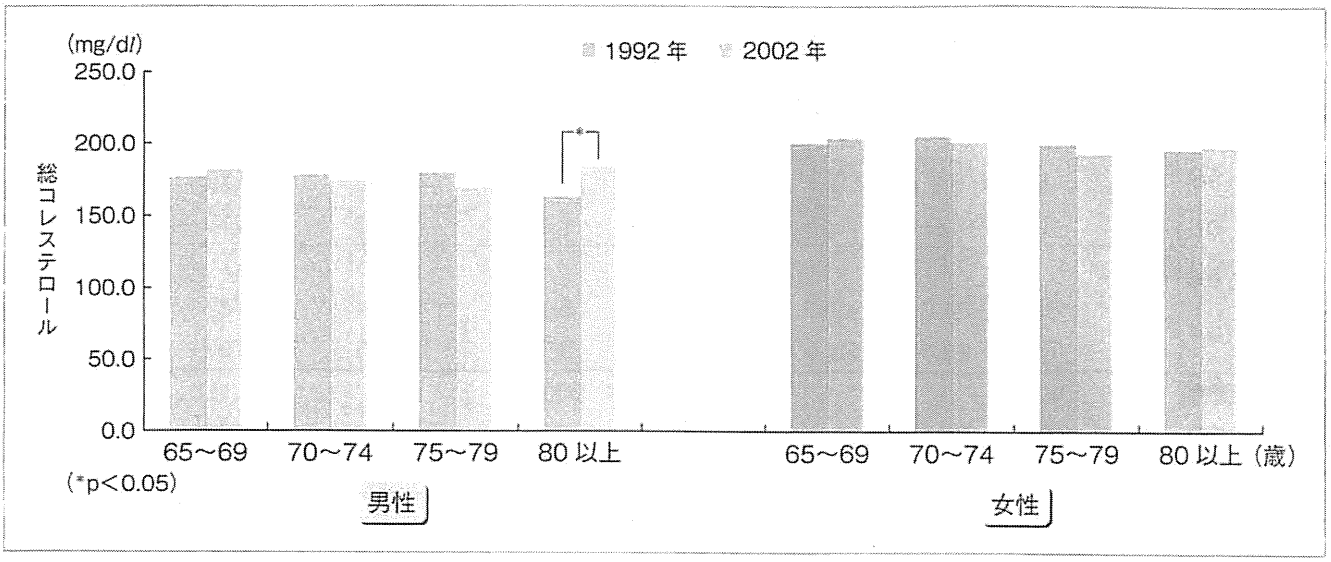
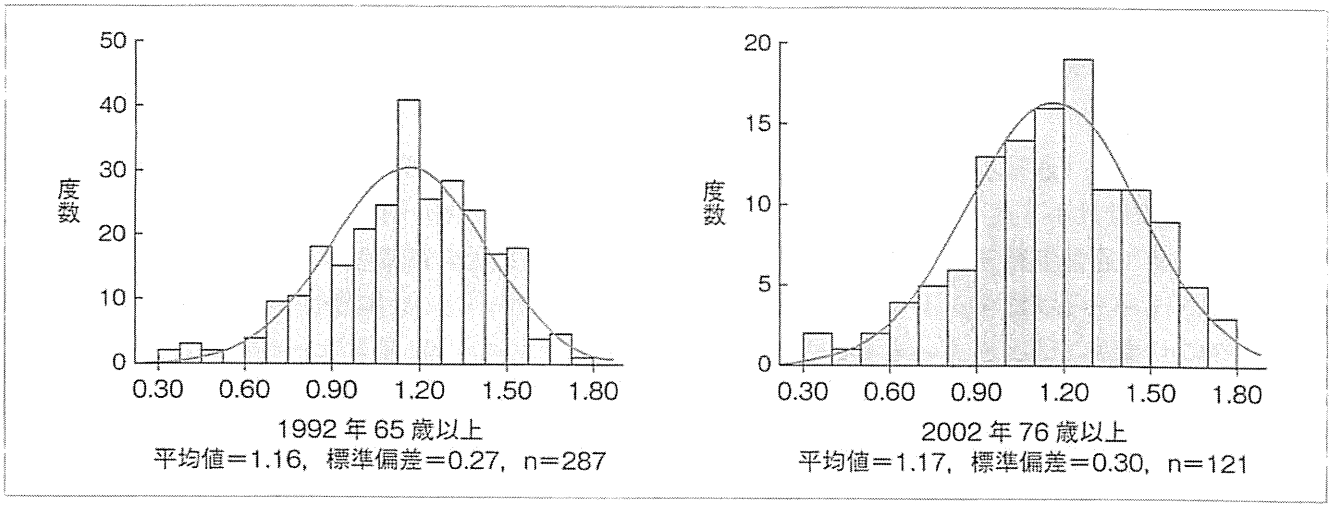


図 11　1992 年コホートと 2002 年コホートで分布に有意差のない事例—通常歩行速度(男性)—



(図 10)．なお，HDL-コレステロールについては男女ともに全年齢階級で '02 年群が有意に高く，HbA1c については男女ともに全年齢階級で有意に低かった．

●2002 年高齢者コホート（'02 年群）は 1992 年高齢者コホート（'92 年群）のいずれの年齢階級と相同の分布を示すか

この分析は，身体的運動能力（握力，開眼片脚起立時間，通常歩行速度，最大歩行速度）について行った．具体的には，各項目について '92 年群(65 歳以上全体）の分布（平均値と標準偏差）を求め，それが '02 年群の何歳以上の分布と有意差がないか（分散についてはF検定を，平均値についてはｔ検定を用いて）分析し，もっともよく近似している年齢層を探索した(図 11)．その結果，男性の開眼片脚起立時間のみ分散に有意差を認めたが，他の項目については分散，平均値ともに有意差の認められない集団の存在することが明らかとなった（表 2)．1 例として，男性の通常歩行速度の '92 年での 65 歳以上の分布と '02 年での 76 歳以上の分布において，分散，平均値ともにまったく有意差のない，相同の正規分布が認められたことを示す（図 11)．

表 2 に示すように，相同分布において男性では最小 4 歳（握力，開眼片脚起立時間，最大歩行速

表2　1992年と2002年コホートで分布（分散と平均値）に有意差のない年齢階層

測定項目	平均値±標準偏差		統計的検定			
	1992年（65歳以上）	2002年（該当年齢とデータ）	F[1]	P値	t[2]	P値
握力						
男	30.2±6.9	69＋ 30.0±6.6	1.925	0.166	0.278	0.781
女	18.2±4.9	75＋ 18.2±5.3	1.405	0.236	0.013	0.990
開眼片脚起立時間						
男	36.6±24.0	69＋ 36.8±23.0	5.155	0.024*	−0.127	0.899
女	25.6±23.0	68＋ 25.8±22.1	2.027	0.155	−0.167	0.868
通常歩行速度						
男	1.16±0.27	76＋ 1.17±0.30	1.861	0.173	−0.304	0.761
女	1.00±0.27	76＋ 1.00±0.27	0.030	0.863	−0.037	0.970
最大歩行速度						
男	1.92±0.44	69＋ 1.92±0.42	1.564	0.212	−0.012	0.990
女	1.56±0.40	73＋ 1.55±0.38	1.910	0.167	0.312	0.755

注1）両コホートの分散についてはF検定を行った．
2）両コホートの平均値についてはt検定を行った．
3）*$p < 0.05$

度）から最大11歳（通常歩行速度）のズレが認められ，女性では最小3歳（開眼片脚起立時間）から最大11歳（通常歩行速度）のズレが認められた．男女でもっとも大きなズレは通常歩行速度（男女ともに11歳）であり，もっとも小さなズレはバランス能力を示す開眼片脚起立時間（男性4歳，女性3歳）であり，今後の高齢者における運動機能向上の取り組みの1つの方向性を示唆しているとも考えられる．いずれにしてもこのような分布のズレは，換言すれば2002年高齢者コホートが最小で3歳，最大で11歳若返っていることを示しており，少なくとも生活機能の基本的要因の1つの因子である身体的運動機能の代表的能力はこの10年間で男女ともに確実に強化され，若返っているとみなしてよいことを意味している．

考察

TMIG-LISAの横断的および縦断的（経年的）データによって，わが国の高齢者の身体機能について概説した．'92年コホートと'02年コホートの比較では，少なくとも握力，歩行速度と運動機能，あるいは血清アルブミン値などは'02年コホートにおいて機能向上やデータ改善が著しく，総じて身体運動機能は向上している．さらに'92年の65歳以上の高齢者コホートに対し，'02年の高齢者コホートの身体機能（とくに運動機能）の測定において，'92年コホートと有意差のない分散と平均値を示す年齢階級を探索した場合，測定項目により多少の変動（3～11歳）は存在するが，男女ともに強化され，若返っていることは確実であると思われる．身体の各機能に着目した場合，バランス能力を表す開眼片脚起立時間は3～4歳程度の若返りであるが，総合的な体力の指標とも考えられている歩行速度は男女ともに10歳ほどの若返りが生じていた．今回得られた長期追跡高齢者集団において，追跡による介入効果がたとえ存在したとしても，いわば新しい高齢者世代では身体の基本的機能が著しく向上・改善したことを示すデータとなっている．

このことは平均寿命の延伸にともなう，若い世代の高齢期への参入は，（一般に喧伝されているような）虚弱化の進んだ高齢社会が必ずしも出現するわけではなく，活力ある高齢社会が（少なくとも当面は）形成されてゆくことを示唆している

ものと思われる.

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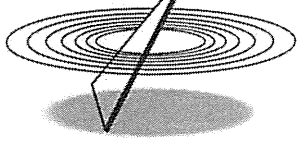
加齢性筋肉減少症(サルコペニア)の診断と治療

Diagnosis and treatment for sarcopenia in the elderly

診断の指針 / 治療の指針



鈴木 隆雄
SUZUKI Takao

1. サルコペニアの疫学(診断も含む)

加齢に伴うサルコペニアは早くから注目され，高齢期の日常生活動作(ADL)や生活の質(QOL)に大きな影響を及ぼすことは知られていた．その原因については，①タンパク質不足や血清ビタミンDレベルの低下等の栄養学的な不良，②性ホルモンやIGF-1等のホルモンの変化，そして③IL-6，IL-10，TNF-α等の炎症性変化などが背景とされている．

高齢期，とくに後期高齢者においては，サルコペニアとなることは避けられず，また必然的に筋力低下を伴う．筋肉量の減少に関する領域あるいはcut-off値については，骨粗鬆症における骨密度と同じ方法で考えることが可能であり，また欧米の多くの研究でもその様式を用いたものが少なくない．すなわち，健全な若年成人(四肢における)筋肉量平均値の2SD以下をサルコペニアと定義して分析するものである．例えばBaumgartnerら[1]はNew Mexico高齢者調査において，883名の対象者にDXA法を用いて測定し，若年平均の2SD以下をサルコペニアと定義したうえで，その出現率は65～70歳では13～24%，80歳以上では50%増加すると報告をしている．

Iannuzzi-Suchichら[2]も同様にDXA法を用いて64～93歳の男女337名を測定し，筋肉量/身長(m)^{2}を求め，やはり若年平均2SD以下をサルコペニアと定義し，その結果，女性の22.6%，男性の26.8%がサルコペニアと判断されたという．さらに彼等のデータでは80歳以上ではおのおの31%，45%に増加している．サルコペニアにおいては上述のように必然的に筋力の低下が伴う．その結果，さまざまな障害が発生することになるが，とくに転倒発生とは関係性が大きい．

また，筋肉の横断面積(cross-sectional area：CSA)による筋肉量の研究も数多くなされている．最近のVisserらの5年間の追跡研究によれば，初回調査時に大腿部CSAの小さい群では5年後の移動能力の障害発生リスクは男性45%，女性34%となっていた[3]．さらにCSA四分位で最低位の者では，ADLの障害が30～40%に上ると報告されている．また，Langらの研究では，膝伸展筋力低下と大腿部CSA低下者では，骨密度とは関係なく，大腿骨頸部骨折発症リスクが50～60%増加することが明らかとなっている[4]．

2. 生活動作からみたサルコペニア

高齢者におけるサルコペニアの診断については従前より単に筋肉量の低下のみならず，筋力低下あるいはそれらに基づく生活動作に強く関与する運動機能の低下を考慮すべきであると考えられていた．最近「ヨーロッパのサルコペニアに関するワーキンググループ(EWGSOP)」[5]より提案されたサルコペニアを判断するアルゴリズムとして，まず歩行速度を測定し，0.8m/秒をcut-off値とし，それ以下にDXA法あるいはBIP法を用いて四肢筋量を測定することを推奨している．広く知られているように，高齢者の歩行速度はその後の生活機能低下や死亡率の予知因子でもあり，サルコペニアの判断にあたっても最初にスクリーニングする方法は妥当性もあるが，EWGSOPの提言するcut-off値(0.8m/秒)は現実にはきわめて遅い値であり，わが国の地域で自立して暮らしている在宅高齢者にあてはめた場合の出現率はほぼ0%に等しく，実際の適用にあたってはわが国固有のcut-off値を設定する必要がある．

3. 虚弱の治療―とくにサルコペニアの予防のための介入研究から

サルコペニアの予防改善については，運動介入や栄養介入等が考えられる．最近筆者らは地域在宅高齢者を対象として，サルコペニアと判定された304名と正常者1,095名の調査項目を比較し，サルコペニア高齢者の特徴を調べ，さらに運動および栄養による同症の改善に関する有効性を確認するためにランダム化比較試験が実施されている[6]．

国立長寿医療研究センター研究所 所長
Key words 虚弱 サルコペニア 運動と栄養 RCT

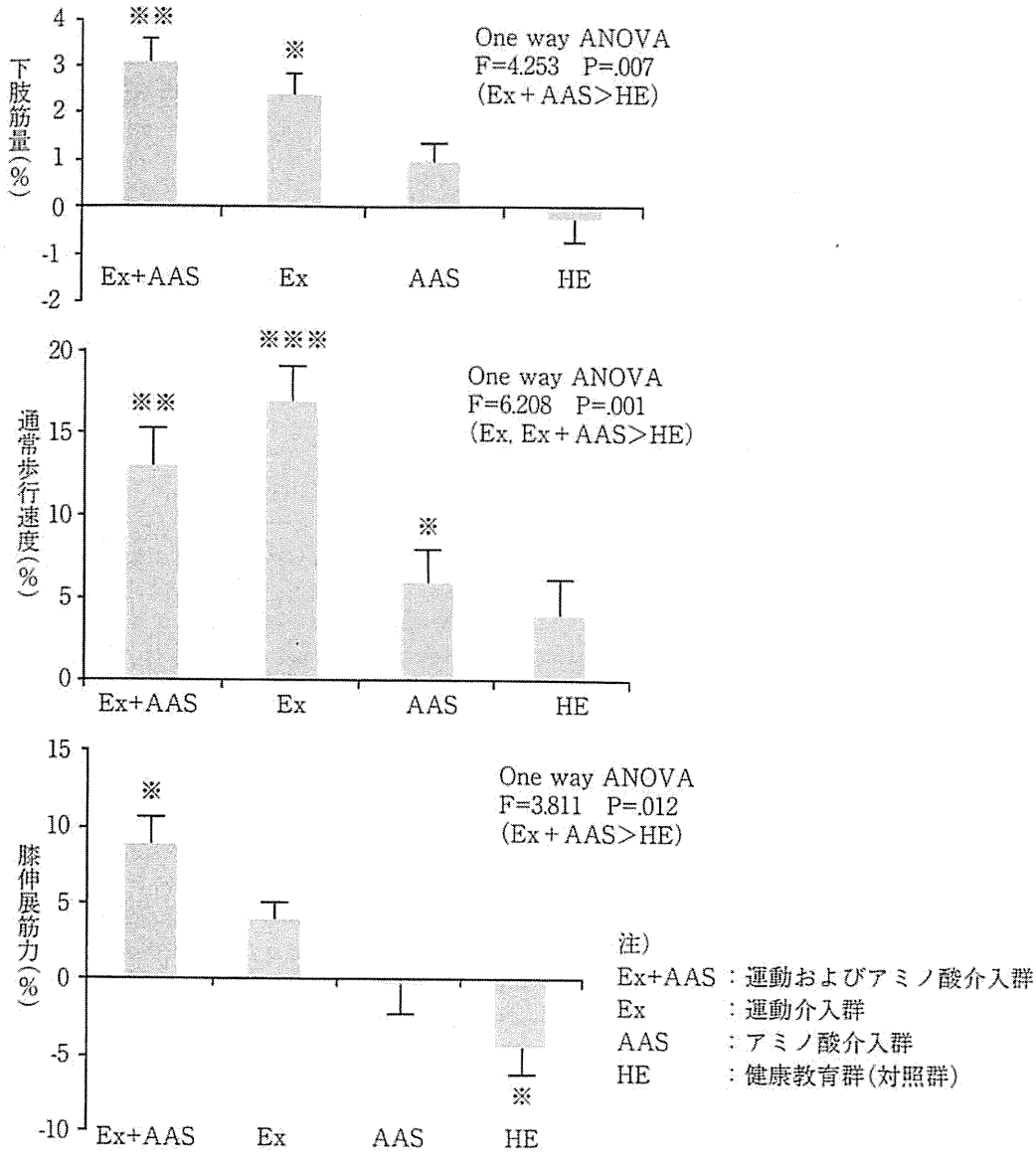


図1　サルコペニア高齢女性に対する運動およびアミノ酸補充による介入(Kim H, Suzuki T, et al：JAGS 2011)

表1　サルコペニア関連変数(筋量，筋力，歩行速度)の組み合わせに対する各介入群の効果

	介入内容						
	HE	ASS		Ex		Ex+AAS	
目的変数	Reference	OR#	95% CI	OR#	95% CI	OR#	95% CI
下肢筋量+膝伸展筋力	1.00	1.99	0.72-5.65	2.61	0.88-8.05	4.89	1.89-11.27
下肢筋量+通常歩行速度	1.00	1.35	0.45-4.08	2.41	0.79-7.58	4.11	1.33-13.68

OR：調製オッズ比　95% CI：95%信頼区間，1＝改善，0＝不変または低下
(HE：健康教育群＝対照群　ASS：アミノ酸補充群　Ex：運動介入群)

(Kim H, Suzuki T, et al：JAGS 2011)

その結果，サルコペニア群と正常群の比較については，サルコペニア群において年齢が高く，下腿三頭筋周囲径，BMI，筋肉量が当然のことながら有意に低値を示すとともに，健康度自己評価，定期的な運動習慣を持っている者の割合も低かった．

次に，サルコペニアと判断される高齢者に対する運動効果とアミノ酸補充効果の検証については，介入参加承諾した者をRCTにより「運動＋栄養群」，「運動群」，「栄養群」および「対照群」の4群に分け，「運動群」には週2回，1回あたり60分間の筋力強化と歩行機能の改善を目的とした包括的運動指導を，「栄養群」にはロイシン高配合のアミノ酸3gを1日2回補充する指導を，「運動＋栄養群」にはその両方を，「対照群」にはこれまで通りの生活を行って頂くよう，それぞれ3ヵ

月間実施した.

その結果，本RCTにおける4群間での介入前後の比較で，下肢筋量および筋力(膝伸展筋力)については「運動群＋栄養群」で最も良く有意に改善し，通常歩行速度においては「運動群」および「運動群＋栄養群」できわめて顕著な改善を示している(図1)．さらに，サルコペニア関連変数の(筋量，筋力，歩速)の組み合わせを目的変数として分析すると，やはり「運動群＋栄養群」で最も強く有意な効果が出現していた(表1)．

このように，身体活動低下や低栄養など可変要因の改善に焦点を当てたRCTによるサルコペニア予防策の効果の検討により，骨格筋量および筋力の増加あるいは生活機能維持に必要な運動能力の可能性が明らかとなった．最近高齢者の筋力低下に基づく運動機能障害や生活機能障害に関して，血中ビタミンD濃度[7)8)]あるいはビタミンC濃[9)]が関与するという報告もあるが，今度臨床的研究データの積み重ねが必要である．現時点では，サルコペニアの予防あるいは改善のためには，運動および栄養を中核とした対策が有効と考えられる．

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Vitamin D Deficiency in Elderly Women in Nursing Homes: Investigation with Consideration of Decreased Activation Function from the Kidneys

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OBJECTIVES: To determine the approximate percentage of women in nursing homes who have vitamin D deficiency and to investigate whether, in assessing vitamin D status in elderly women, there are problems with measuring only 25 hydroxy-vitamin D_3 ($25(OH)D_3$) and whether decreased vitamin D activation as a result of poor renal function needs to be considered.

DESIGN: Cross-sectional study.

SETTING: Forty-eight nursing homes in Japan.

PARTICIPANTS: Four hundred three women with a mean age of 86.5 living in nursing homes who had participated in a clinical trial for hip protectors and were not bedridden.

MEASUREMENTS: At the start of the trial, in addition to general biochemical data, $25(OH)D_3$, 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$), intact parathyroid hormone (intact PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked *N*-telopeptide of type I collagen (NTx), and osteocalcin were measured in participants' blood, and statistical analysis was performed.

RESULTS: $25(OH)D_3$, which is thought to reflect vitamin D status in the body, was surveyed and found to have a mean value of 16.7 ng/mL. $25(OH)D_3$ was less than 16 ng/mL in 49.1% of all participants. Creatinine clearance (CCr) was less than 30 mL/min in 20.1% of participants. Participants with serum $25(OH)D_3$ less than 16 ng/mL and CCr less than 30 mL/min had significantly higher levels of intact PTH and serum NTx. Participants with a CCr less than 30 mL/min had significantly lower levels of $1,25(OH)_2D_3$.

CONCLUSION: Frail elderly adults living in nursing homes with poor renal function had lower $1,25(OH)_2D_3$ and higher intact PTH levels and were thus thought to have poorer vitamin D activating capacity. Supplementation with cholecalciferol may be insufficient in people who have poor renal function. **J Am Geriatr Soc 60:251–255, 2012.**

Key words: 25-hydroxy-vitamin D_3; 1,25-dihydroxy-vitamin D_3; nursing homes

The importance of vitamin D for bones has been indicated in previous studies.[1,2] Frail elderly adults with limited ability to perform activities of daily living (ADL) who enter a nursing home are at high risk for low vitamin D as a result of poor nutrition and lack of sunlight. Vitamin D deficiency is an important risk factor for osteoporosis and fractures from falls in elderly adults.[3–5] When assessing serum 25 hydroxy-vitamin D_3 ($25(OH)D_3$) levels to define vitamin D deficiency, many reports have adopted a cutoff of 20 ng/mL.[6–8] It has also been reported that individuals with hip fracture or those with a history of falls have low $25(OH)D_3$ levels.[9,10] Secondary hyperparathyroidism from poor renal function in elderly adults must also not be overlooked.[11] The group that is probably at the highest risk of falls and fractures is elderly women living in nursing homes who are not completely bedridden but have a mobility level of at least being able to move about in a wheelchair with assistance. The participants in this study were such a group of people, who had previously participated in a fracture prevention trial using hip protectors.[12] Vitamin D levels, renal function, and the relationship between the two were investigated in these women, and the approximate percentage of these nursing home residents who needed supplemental vitamin D was considered.

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METHODS

Participants were 403 women aged 70 and older (range: 70–103) who lived in 48 nursing homes from whom consent was obtained for participation in a fracture prevention trial using hip protectors.[12] They had a mobility level of at least being able to move about in a wheelchair with assistance. A history of bilateral hip fracture was a condition for exclusion. Written informed consent was obtained from all participants. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study. Blood was collected from participants as the 48 nursing homes in the southern part of central Japan were visited in turn between January 2005 and May 2008. At the start of the trial, in addition to general biochemical data, 25(OH)D_3, 1,25-dihydroxy-vitamin D_3 (1,25 $(OH)_2D_3$), intact parathyroid hormone (PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked *N*-telopeptide of type I collagen (NTx), and osteocalcin were measured using participants' blood, and statistical analysis was performed. 25(OH)D_3 was measured using the radioimmunoassay double antibody method. Frail elderly adults have little muscle, and even if creatinine (Cr) is in the normal range, it cannot be concluded that renal function is normal. For a simpler assessment of renal function, we estimated Cr clearance (CCr) with adjustments for age and body weight using the widely adopted Cockcroft-Gault formula.[13]

Statistical Analyses

SPSS (version 17.0, SPSS, Inc., Chicago, IL) was used in the statistical analysis. Adjustment was made for age as a control variable in partial correlation. Two-tailed significance probability <.05 was taken to be significant. The Student *t*-test was used to test for differences between the mean values of the two groups, with $P < .05$ taken to indicate significance. The Bonferroni test was used to compare the mean values in the groups, using a general linear model adjusted for age. $P < .05$ was taken to indicate a significant difference.

RESULTS

Participants were aged 70 were to 103 (mean 86.5). Mean 25(OH)D_3 level, which is an indicator of vitamin D level, was low (16.7 ng/mL). The mean values for the following tests were: 1,25$(OH)_2D_3$, 44.4 ± 17.5 pg/mL; intact PTH, 57.4 ± 38.7 pg/mL; BAP, 32.4 ± 13.2 U/L; osteocalcin, 7.8 ± 3.8 ng/mL; and NTx, 17.6 ± 9.7 nmol bone collagen equivalent/L. The percentile distribution in the 25(OH)D_3 distribution is shown in Figure 1. When 25(OH)D_3 concentration of less than 20 ng/mL was taken to indicate vitamin D deficiency, 78.1% of participants were found to be vitamin D deficient.

To further investigate 25(OH)D_3, the partial correlation was first examined adjusted for age. There were significant positive correlations between 25(OH)D_3 and 1,25$(OH)_2D_3$ (correlation coefficient $(r) = 0.149$, $P = .003$), albumin ($r = 0.185$, $P < .001$), total cholesterol ($r = 0.165$, $P = .001$), blood urea nitrogen ($r = 0.116$, $P = .02$), Ca ($r = 0.153$, $P = .002$), and P ($r = 0.100$, $P = .04$). Significant negative correlations were shown with serum NTx ($r = -0.153$, $P = .002$) and intact PTH ($r = -0.178$, $P < .001$). It was then decided to further investigate intact PTH, which had shown a high correlation. Mean intact PTH levels in the group with a serum 25 $(OH)D_3$ concentration less than 12.0 ng/mL, 12.0 to 15.9 ng/mL, and 16.0 ng/mL or higher were 72.3 pg/mL, 60.4 pg/mL, and 51.1 pg/mL, respectively. Mean intact PTH level was significantly higher in participants with a serum 25(OH)D_3 concentration less than 12.0 ng/mL ($P < .001$) and 12.0 to 15.9 ng/mL ($P = .02$) than in those with a concentration of 16.0 ng/mL or higher. Participants younger than 85 were then compared with those aged 85 and older to determine whether the various data differed depending on age (Table 1). Significant differences were seen in 25(OH)D_3, 1,25$(OH)_2D_3$, and intact PTH. Because 1,25$(OH)_2D_3$, a form of activated vitamin D, also decreases with age, it was decided to investigate 1,25 $(OH)_2D_3$. First, in the age-adjusted partial correlation, 1,25$(OH)_2D_3$ showed the strongest negative correlation with Cr ($r = -0.323$, $P < .001$). This finding suggests that renal function strongly affects 1,25$(OH)_2D_3$. The relationship between 1,25$(OH)_2D_3$ concentration and estimated CCr is shown in Table 2. 1,25$(OH)_2D_3$ concentration was significantly lower in participants with CCr less than 30 mL/min. Similarly, intact PTH concentration was significantly higher in participants with CCr less than 30 mL/min, in whom 1,25$(OH)_2D_3$ concentration was significantly lower (Table 2). A tendency was seen for 25(OH) D_3 levels to be higher with lower CCr, and a significant difference was seen between groups with CCr of less than 30 and 45 mL/min or greater ($P < .05$, general linear model Bonferroni test). To improve understanding of how participants were distributed according to 25(OH)D_3 concentration and CCr value, they were divided into four groups with 25(OH)D_3 concentrations of less than 16 and 16 ng/mL and greater and CCr of less than 30 and 30 mL/min and greater. Concentrations of 1,25$(OH)_2D_3$, intact PTH, and serum NTx of the groups were then compared (Table 3). Of 198 participants with 25(OH)D_3 concentrations of less than 16 ng/mL, 36 (18.4%) had poor renal function (CCr < 30 mL/min), and of 205 participants with

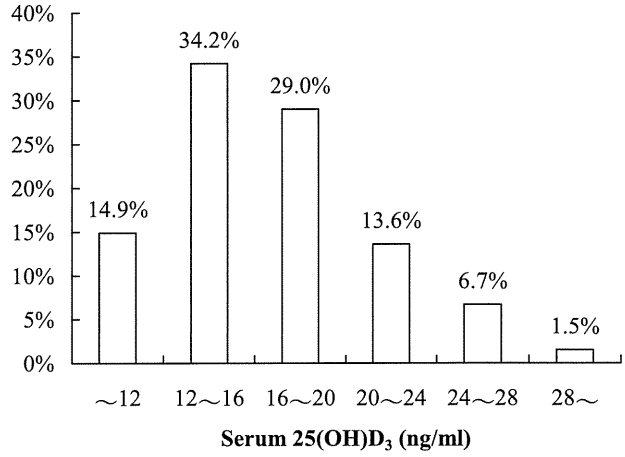

Figure 1. Percentile distribution of serum 25 hydroxy-vitamin D_3 (25(OH)D_3) concentrations. 25(OH)D_3 level was < 20 ng/mL in 78.1% and < 16 ng/mL in approximately half.

Table 1. Comparison of Mean Data Values According to Age

Characteristic	Normal Range	Mean ± Standard Deviation <85 (n = 139)	Mean ± Standard Deviation ≥85 (n = 264)	*P*-Value
Age	—	79.1 ± 3.8	90.4 ± 3.7	<.001
Height, cm	—	145.2 ± 7.5	142.8 ± 7.2	.003
Weight, kg	—	44.1 ± 8.3	41.6 ± 7.5	.003
Body mass index, kg/m^2	—	20.7 ± 4.4	20.0 ± 3.3	.28
25 hydroxy-vitamin D_3, ng/mL	—	17.5 ± 4.9	16.3 ± 4.7	.01
1,25-dihydroxy-vitamin D_3, pg/mL	20–60	47.5 ± 18.1	42.7 ± 16.9	.008
Intact parathyroid hormone, pg/mL	10–65	51.6 ± 27.4	60.4 ± 43.2	.03
Albumin, g/dL	3.9–4.9	3.9 ± 0.3	3.9 ± 0.4	.01
Total protein, g/dL	6.5–8.2	6.9 ± 0.5	6.9 ± 0.5	.26
Total cholesterol, mg/dL	120–220	207.6 ± 38.0	195.9 ± 36.3	.003
Blood urea nitrogen, mg/dL	8–20	17.8 ± 6.5	18.7 ± 7.7	.25
Creatinine, mg/dL	0.5–0.8	0.66 ± 0.3	0.72 ± 0.4	.13
Creatinine clearance (Cockcroft-Gault formula), mL/min	—	55.2 ± 18.6	38.9 ± 12.7	<.001
Glomerular filtration rate (modified diet in renal disease formula), mL/min	—	73.9 ± 25.0	65.4 ± 22.1	.001
Calcium, mg/dL	8.7–10.1	8.8 ± 0.4	8.8 ± 0.5	.25
Phosphorus, mg/dL	2.5–4.5	3.6 ± 0.4	3.6 ± 0.5	.21
Aspartate aminotransferase, U/L	10–40	19.2 ± 6.2	19.7 ± 6.2	.39
Alanine aminotransferase, U/L	5–45	13.2 ± 7.5	11.5 ± 6.0	.02

Table 2. Comparison of 1,25-Dihydroxy-Vitamin D_3 ($1,25(OH)_2D_3$), Intact Parathyroid Hormone (PTH), and 25 Hydroxy-Vitamin D_3 ($25(OH)D_3$) Concentrations According to Creatinine Clearance (CCr)

CCr, mL/min	Mean (Standard Error) $1,25(OH)_2D_3$, pg/mL	Intact PTH, pg/mL	25 Hydroxy-Vitamin D_3, ng/mL
<30.0 (n = 82)	33.0 (1.9)*	80.1 (4.3)*	17.9 (5.2)
30.0–44.9 (n = 160)	45.8 (1.3)	52.7 (3.0)	17.0 (4.9)
≥45 (n = 161)	48.8 (1.4)	50.5 (3.2)	15.9 (4.4)

* $P < .05$, general linear model Bonferroni test.

Table 3. Comparison of 1,25-Dihydroxy-Vitamin D_3 ($1,25(OH)_2D_3$), Intact Parathyroid Hormone (PTH), and Cross-Linked *N*-Telopeptide of Type I Collagen (NTx) Concentrations According to Creatinine Clearance (CCr) and 25 Hydroxy-Vitamin D_3 ($25(OH)D_3$) Concentration

CCr, mL/min	Mean (Standard Error) $25(OH)D_3$, ng/mL <16	$25(OH)D_3$, ng/mL ≥16
<30		
$1,25(OH)_2D_3$, pg/mL	29.0 (2.7)*	36.3 (2.5)*
Intact PTH, pg/mL	104.8 (6.1)*	60.7 (5.4)
NTx, nmolBCE/L	28.3 (1.6)*	18.9 (1.4)
≥30		
$1,25(OH)_2D_3$, pg/mL	45.2 (1.2)	49.3 (1.3)
Intact PTH, pg/mL	55.1 (2.8)	48.1 (2.9)
NTx, nmolBCE/L	17.1 (0.7)	15.3 (0.7)

$1,25(OH)_2D_3$ levels were significantly lower in participants with CCr lower than 30 mL/min than those with CCr of 30 mL/min and higher. Mean intact PTH and NTx concentrations in participants with CCr lower than 30 mL/min and $25(OH)D_3$ of less than 16 ng/mL were significantly higher than in the other participants.

* $P < .05$, general linear Bonferroni test.

$25(OH)D_3$ concentrations of 16 ng/mL and higher, 45 (22.0%) had poor renal function. These percentages were approximately the same, but concentrations of intact PTH and NTx were significantly higher in the group with $25(OH)D_3$ of less than 16 ng/mL and CCr of less than 30 mL/min. In addition, in the group with CCr of less than 30 mL/min, $1,25(OH)_2D_3$ concentration was significantly lower than in the group with CCr of 30 mL/min and higher, regardless of $25(OH)D_3$ concentration.

DISCUSSION

Table 4 summarizes the reports on $25(OH)D_3$ concentration in elderly cohorts.[14–20] A comparison of reports in which participants were living in institutions and reports in which participants were living independently revealed lower levels of $25(OH)D_3$ in residents of institutions, who are thought to have greater difficulty with activities of daily living. Experts have proposed that $25(HO)D_3$ concentrations of 20 to 32 ng/mL, or roughly 30 ng/mL, are the minimum necessary concentration to prevent fractures.[21] A recent meta-analysis also reported that concentrations of 75 to 100 nmol/L balanced the benefits and risks of the health of elderly people.[22] Many studies take PTH to be an indicator of the cutoff value for $25(OH)D_3$ concentration.[6–8] When PTH is taken as an indicator, a $25(OH)D_3$ concentration of 20 ng/mL is taken as the cutoff

Table 4. Past Reports of 25 Hydroxy-Vitamin D_3 (25 $(OH)D_3$) Levels in Elderly Cohorts

Study Participants	n	Age, Mean	25(OH)D_3, ng/mL, Mean	References
Nursing home (Japan)	133	84.6	11.9	14
Nursing home or housebound (United States)	116	81	12.6	15
Nursing home (this study, Japan)	425	86.4	16.8	—
Nursing home (United States)	35	74	17.4	16
Independent women (Canada)	186	73	15.6	17
Independent women (France)	440	80	17.0	18
Community-dwelling elderly women (Japan)	2,007	75.4	24.2	19
Independent women (United States)	500	71	29.6	20

in many reports.[6–8] In the participants in this study, 78.1% had 25(OH)D_3 levels less than 20 ng/mL. Another study reported that 25(OH)D_3 of 20 ng/mL and greater is needed when intact PTH is taken as the indicator and that 28 ng/mL and greater is needed when bone density in the femoral neck is taken as the indicator.[6] From the present results, the cutoff value for 25(OH)D_3 as an indicator of intact PTH was thought to be 16 ng/mL; 49.1% of participants had 25(OH)D_3 of less than 16 ng/mL (Figure 1). In general, people with poor renal function have lower levels of 1,25$(OH)_2D_3$, an activated form of vitamin D, as a result of poor vitamin D activating capacity. Moreover, secondary hyperparathyroidism from poor renal function is not unusual in elderly people.[11] In the present results as well, there was a strong negative correlation between 1,25 $(OH)_2D_3$ and CCr ($r = -0.323$, $P < .001$), which suggests that renal function strongly affects 1,25$(OH)_2D_3$. As shown in Table 2, intact PTH levels were significantly higher and 1,25$(OH)_2D_3$ significantly lower with a CCr of less than 30 mL/min. From this it can be conjectured that vitamin D activation in the kidneys may decrease in cases of secondary hyperparathyroidism from poor renal function. In addition, as shown in Table 3, the percentage of people with poor renal function (CCr < 30 mL/min) was nearly the same in participants with 25(OH)D_3 levels greater and less than 16 ng/mL. Women with such vitamin D activating capacity made up 20.1% of all participants, although according to guidelines published in the United States in 2003[23] for bone metabolism disorders in individuals with chronic kidney disease, if PTH is measured and found to be high in people undergoing dialysis and those with chronic renal failure with less than 60% renal function, it is recommended that serum 25(OH)D_3 be measured and vitamin D_2 be administered if it is less than 30 ng/mL. Considering these guidelines, a greater number of people would probably be judged to have poor renal function, although there are limitations to this investigation. All CCr values were derived through calculation, not from actual measurements of CCr or glomerular filtration rate (GFR). Cystatin C was not measured either. The Cockcroft-Gault formula was first used to calculate CCr, but the Modification of Diet in Renal Disease (MDRD) formula[24] was also used to investigate CCr. The correlation between CCr calculated using the Cockcroft-Gault formula and GFR calculated using the MDRD formula was high ($r = 0.769$, $P < .001$). Moreover, in the group with GFR of less than 50 mL/min (n = 84, 20.8%), a significant difference, similar to that in the results obtained with the Cockcroft-Gaults formula, was seen. Thus, although CCr obtained from calculations is not ideal, it seems to be reliable. In addition, intact PTH level may be a useful indicator in establishing a cutoff value for 25(OH) D_3 in frail elderly adults such as the present participants. Moreover, because plainly higher intact PTH levels were shown in participants with poor vitamin D activation in the kidneys, intact PTH may have an important role in considering vitamin D supplementation in frail elderly adults. Many experts recommend vitamin D supplementation with cholecalciferol when 25(OH)D_3 level drops below 30 to 32 ng/mL. A recent Institute of Medicine report[25] recommends supplementation when 25(OH)D_3 is less than 20 ng/mL, but it does not specifically address frail elderly adults. Vitamin D is not activated efficiently even with cholecalciferol supplementation in frail elderly adults, such as the present participants, who seem to have poor activation of vitamin D. Theoretically, therefore, it would seem that supplementation with a form of activated vitamin D such as paricalcitol or alfacalcidol may be beneficial in the case of frail elderly adults with poor renal function.

CONCLUSION

In this study, 25(OH)D_3 levels were found to be low in women living in nursing homes who were at least able to move about in a wheelchair with assistance. Approximately 50% to 80% of participants were thought to be vitamin D deficient, although this depends somewhat on the cutoff value used for 25(OH)D_3. In addition, approximately 20% of all participants were thought to have decreased vitamin D activating capacity in the kidneys. Such poor vitamin D activation capacity in the kidneys was present in a similar 20% of people whose 25(OH)D_3 level was above the cutoff level (16 ng/mL). An unexpectedly large number of women in nursing homes thus had poor vitamin D activation secondary to poor renal function. For vitamin D supplementation, therefore, it may be necessary to make a comprehensive judgment with measurements of intact PTH and CCr or GFR and 1,25 $(OH)_2D_3$ rather than cholecalciferol supplementation based simply on 25$(OH)_3$ level.

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ORIGINAL ARTICLE

Serum 25-hydroxyvitamin D status in hip and spine-fracture patients in Japan

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Abstract
Background Serum 25-hydroxyvitamin D (25(OH)D) is used as an index that reflects the level of vitamin D. We have previously reported, on the basis of a study in Sado in Niigata, that patients with hip fracture have lower serum 25(OH)D levels than non-hip-fracture cases. In this study, the serum 25(OH)D status in hip-fracture cases was examined in four regions in Japan. Although most hip-fracture patients have experienced past spine-compression fractures, the relationship of these fractures and 25(OH)D is unknown. Therefore, we also examined the 25(OH)D level in spine-compression fracture patients in the same locations and time periods.
Methods The levels of 25(OH)D, intact parathyroid hormone (intact PTH), undercarboxylated osteocalcin (ucOC), urine *N*-terminal crosslinking telopeptide of type I collagen (NTX), and bone mineral density were examined in patients with hip and spine fracture due to osteoporosis in several regions in Japan.
Results There were no significant differences in age, BMI, serum 25(OH)D, serum intact PTH, and serum ucOC among the regions. Levels of serum 25(OH)D were low in patients with hip fracture and spine fracture. The average serum 25(OH)D level was significantly lower in hip-fracture patients than in spine-fracture patients (16.3 vs. 18.1 ng/mL, $P < 0.05$). High serum ucOC was found in 37% of hip-fracture patients and 44% of spine-fracture patients.
Conclusions Both hip and spine-fracture patients have vitamin D insufficiency, with similar results found in elderly patients in four areas of Japan. The severity of this condition tends to be more serious in hip-fracture patients than in spine-fracture patients.

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Introduction

Osteoporosis causes fractures, serious physical and mental damage, and decreased activities of daily living (ADL) and quality of life (QOL). Hip fractures and vertebral compression fractures are especially common in elderly people [1, 2], and the negative effects of these fractures on ADL and QOL emphasize the need to determine the associated

Table 1 Number of patients in the study

	Hip fracture					Spine fracture				
	Sado	Aichi	Tottori	Kumamoto	Total	Sado	Aichi	Tottori	Kumamoto	Total
Male	14	11	12	15	52	4	6	2	0	12
Female	52	37	26	58	173	27	14	11	0	52
Total	66	48	38	73	225	31	20	13	0	64

risks and causes and to establish preventive measures. A relationship between serum vitamin D (25(OH)D; 25-hydroxyvitamin D) level and hip fracture has been established. Overseas [3, 4] and domestic reports, including an epidemiologic survey in Sado City in Niigata Prefecture in 2004 [5], have shown that 25(OH)D is significantly lower in hip-fracture patients than in controls. Furthermore, half of Japanese women aged >65 years old also have insufficient levels of serum 25(OH)D [6, 7], and this may be a major risk factor for hip fracture.

Epidemiologic surveys suggest that the incidence of hip fracture is lower in Japan than in Europe and the United States [8–10], and there are also regional differences in Japan. Furthermore, because most hip-fracture patients (81.8%) have past vertebral compression fracture on X-ray [5], the relationship of compression fracture and serum 25(OH)D is of concern. In this study, the relationship between serum 25(OH)D and hip fracture was examined from a perspective of regional differences in Japan. We also aimed to clarify the relationship between spine fracture and serum vitamin D level, and to examine the vitamin K status of patients with hip fracture or spine fracture.

Patients and methods

Study site

A survey of patients treated for hip fracture and spine-compression fracture was performed in one or two hospitals in several areas of Japan: Niigata (Sado), Aichi, Tottori, and Kumamoto prefectures.

Subjects

The subjects were inpatients and outpatients aged ≥65 years old with fresh hip and spine-compression fracture treated from April 1, 2007 to March 31, 2008. All patients gave consent to the study. For compression fracture, it was not always easy to identify a new fracture. However, patients who visited the hospital for symptoms such as back pain and were judged, on the basis of X-ray and physical examination by an orthopedic doctor, to have a fresh vertebral fracture were considered as a case of new fracture (an incident of fracture: clinical fracture).

There were 102, 81, 57, and 90 subjects from Sado, Aichi, Tottori, and Kumamoto, respectively. Of these 330 patients, 16 with a tumor, osteomalacia, bone fracture due to systemic diseases, hyperthyroidism, hyperparathyroidism, renal failure, or dialysis were excluded. This left 314 patients (66 males, 247 females, 1 unknown) for whom data were collected. Of these patients, data were analyzed for 289 (225 cases of hip fracture and 64 of spine fracture; Table 1) after exclusion of patients who had taken drugs such as active vitamin D, vitamin K, and bisphosphonate, and one patient of unknown sex.

There were more patients with hip fracture than with spine-compression fracture in this study. Epidemiologically, there were more patients with spine fracture than hip fracture, but those with spine fracture were mainly outpatients. This reduced the number of cases of spine fracture in the analysis, and there was no selective exclusion of spine-fracture patients in the study.

Measurements

Data were collected for body height and weight (body mass index, BMI), serum 25(OH)D, serum intact PTH (intact parathyroid hormone), urine NTX (*N*-terminal crosslinking telopeptide of type I collagen), serum undercarboxylated osteocalcin (ucOC), bone mineral density (BMD) in the hip, and history of fractures of other bones, including the spine, hip, distal radius, and proximal humerus. Blood samples for biochemical assays were collected within 1 week after fracture. The exact date of spine fracture was often uncertain, but most data were collected within 1 week after the first medical examination.

The serum 25(OH)D level was measured by enzyme-linked immunosorbent assay (ELISA) assay using a kit supplied by DiaSorin (Stillwater, MN, USA). A serum 25(OH)D level of at least 15–20 ng/mL is needed to optimize PTH levels, on the basis of several reports. Hollis et al. [11] found that the normal range of 25(OH) D was 32–100 ng/mL and that a concentration of <10 ng/mL indicated a vitamin D-deficient state. Other studies performed in the USA and Australia [12, 13] show that a serum 25(OH) D level of at least 15–20 ng/mL is needed to

achieve an optimum PTH level, and therefore we defined a 25(OH) D level of <20 ng/mL as vitamin D insufficiency.

Serum-intact PTH was measured by means of an electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Basel, Switzerland), in which intact PTH molecules are detected; the normal range is 10–65 pg/mL [14, 15]. We note that Segersten et al. [16] have suggested that the upper limit of the normal range for PTH may be too high; however, LeBoff et al. [4] used a value of 65 pg/mL, and we also chose 65 pg/mL as the upper limit of the normal range for intact PTH.

The urine NTX assay was performed using an Osteomark NTX ELISA kit (Inverness Medical Professional Diagnostics, Princeton, NJ, USA). Serum ucOC was measured by ECLIA (Sanko Junyaku, Tokyo, Japan). A high level of serum ucOC is a reported risk factor for hip fracture [17, 18]. In patients with vitamin K insufficiency, osteocalcin (OC) (a basic bone protein produced by osteoblasts) is released into blood as ucOC, which has a glutamic acid (Glu) residue that is not converted to a γ-carboxyl glutamate. This reduces OC incorporation into bone. The cutoff value for serum ucOC is 4.5 ng/mL [19, 20].

BMD of the hip was measured by dual-energy X-ray absorptiometry (DXA) (in Sado: Hologic 4500A, Bedford, MA, USA; in Aichi: DPX-NT; GE Medical Systems Lunar, Madison, WI, USA; in Kumamoto: Hologic Delphi, Bedford, MA, USA). In hip-fracture cases, BMD was measured in the hip on the opposite side to the fractured hip. Data for past fractures of the hip, spine, distal radius, and proximal humerus were determined by interview or X-ray.

Statistical analysis

Comparison between two groups was performed using a non-paired t test for parametric variables and a Mann–Whitney U test for non-parametric variables. Comparison among multiple groups was performed using ANOVA, followed by a Tukey test for parametric variables and a Kruskal–Wallis test for non-parametric variables. Analysis was performed using Microsoft Excel 2007 and Ekuseru Toukei 2008 for Windows.

Ethical considerations

The study plan was approved by the Japanese Orthopedics Association Ethical Review Board. The study was explained in writing to the patients and informed consent was obtained.

Results

Data were collected for 66 cases of hip fracture (52 females and 14 males) and 31 of spine-compression fracture (27 females and 4 males) in Sado City, Niigata (an island city) (Table 1); for 48 cases of hip fracture (37 females, 11 males) and 20 of spine fracture (14 females and 6 males) in Aichi Prefecture (National Center for Geriatrics and Gerontology); for 38 cases of hip fracture (26 females and 12 males) and 13 of spine fracture (11 females and 2 males) in Tottori Prefecture (including patients in three hospitals); and for 73 cases of hip fracture (58 females and 15 males) and 0 of spine fracture in Kumamoto Prefecture (Tamana Central Hospital).

Data in the four regions

The average values of variables in each region are shown in Table 2. The average age at the time of injury ranged from 82 to 84 years old for hip-fracture cases, with no significant differences among the regions. For BMI in hip-fracture patients also there were no significant differences among regions. The order of BMI in spine fracture was Tottori > Sado > Aichi, with no significant differences among regions. The average levels of serum 25(OH)D (<17 ng/mL) in hip-fracture patients were low in all four areas. These values were especially low in Sado and Aichi, but there were no significant differences among the regions. The mean serum 25(OH)D level was 17–19 ng/mL in spine-fracture cases, and was lowest in Sado, but again with no significant regional differences.

The average serum intact PTH level (>45 pg/mL) in hip-fracture patients was comparatively high in all four areas, with no significant regional differences. This level ranged from 40 to 47 pg/mL in spine-fracture patients, and there were also no significant differences among the areas.

In patients with hip fracture, urine NTX was significantly higher in Aichi and Sado than in Kumamoto ($P < 0.01$ and $P < 0.05$, respectively). There were no significant differences in urine NTX in spine-fracture patients among the regions.

Data for serum ucOC were collected from Sado, Tottori, and Kumamoto, and showed no significant differences among these areas. BMD analysis was performed in Sado, Aichi, and Kumamoto. Because radial and spine BMD were measured in Tottori, we excluded these data from the analysis. BMD in hip-fracture patients in Sado was significantly lower than that in Aichi ($P < 0.001$). There were no significant differences in BMD in spine-fracture patients among the regions.

Comparison of hip and spine fracture

A comparison of variables in hip and spine-fracture cases is shown in Table 3. The average age over all regions was significantly higher for hip fracture than for spine fracture (83.0 vs. 80.1 years old, $P < 0.01$). BMI showed no

Table 2 Average values of variables for cases of hip and spine fracture in each region (mean ± SD)

	Variables/ Regions	Age (years old)	BMI (kg/m²)	Serum 25(OH)D (ng/mL)	Serum intact PTH (pg/mL)	Urine NTX-cre (nmol BCE/nmol Cr)	Serum ucOC (ng/mL)	BMD (g/cm2)
	Sado	84.3±7.83	20.1±3.34	16.0±5.61	55.0±53.6	98.6±52.5	4.48±4.49	0.465±0.164
Hip fracture	Aichi	82.2±9.38	19.6±4.01	15.5±4.88	46.8±19.04	107.6±63.8	-	0.585±0.144
(*n*=225)	Tottori	83.2±8.07	21.2±3.64	17.1±5.41	46.3±23.6	84.0±46.2	4.57±3.34	-
	Kumamoto	82.3±11.5	20.2±3.05	16.9±4.48	59.7±31.5	73.7±42.5	4.61±4.50	0.535±0.140
	Sado	79.6±6.67	21.8±5.56	17.5±6.00	47.3±18.1	76.8±46.8	6.61±5.59	0.522±0.164
Spine fracture	Aichi	81.7±5.85	20.3±6.04	19.2±5.05	41.9±22.1	92.8±44.4	-	0.590±0.203
(*n*=64)	Tottori	79.2±5.85	22.4±2.49	17.7±5.5	43.7±17.0	67.7±26.2	5.18±2.83	-
	Kumamoto	-	-	-	-	-	-	-

* $P < 0.05$, ** $P < 0.01$

Table 3 Average values of variables for cases of hip and spine fracture

Variables	Hip fracture	Spine fracture	*P* value
Age (years old)	83.0 ± 9.51	80.1 ± 6.26	$P < 0.01$
BMI (kg/m²)	20.5 ± 3.49	21.4 ± 5.15	n.s.
Serum 25-OHD (ng/mL)	16.3 ± 5.13	18.1 ± 5.59	$P < 0.05$
Serum intact PTH (pg/nL)	53.3 ± 36.8	44.9 ± 19.1	n.s.
Urine NTX (nmol BCE/nmol Cr)	89.9 ± 53.5	80.5 ± 42.9	n.s.
Serum ucOC (ng/mL)	4.55 ± 4.25	6.18 ± 4.95	$P < 0.01$
BMD (g/cm²)	0.521 ± 0.163	0.616 ± 0.136	$P < 0.01$

significant difference between hip and spine cases, but the average BMI in spine-fracture patients tended to be higher than that in hip-fracture patients. The average 25(OH)D level in hip-fracture patients was significantly lower than that in spine-fracture patients (16.3 vs. 18.1 ng/mL, $P < 0.05$). There were no significant differences in intact PTH between hip and spine-fracture cases, but the average intact PTH in hip-fracture patients tended to be higher than that in spine-fracture patients.

Urine NTX was elevated in both fracture types, with no significant difference between the two types. The average serum ucOC level was significantly lower in patients with hip fracture than in those with spine fracture (4.55 vs. 6.18 ng/mL, $P < 0.01$). BMD was low for both types of fracture, and mean BMD for all hip-fracture cases was significantly lower than that for all spine-fracture cases (0.521 vs. 0.616 mg/cm², $P < 0.001$).

The percentages of patients with 25(OH)D <20 ng/mL were 79.0% for hip-fracture cases and 66.7% for spine-fracture cases (Fig. 1). Data for ucOC were available for Sado, Tottori, and Kumamoto. In these regions, the percentages of patients with ucOC ≥ 4.5 ng/mL were 36.2% in hip-fracture cases and 50.0% in spine-fracture cases (Fig. 2).

Past fractures

For evaluation of past fracture, asymptomatic spine-compression fracture was evaluated on the basis of X-ray only in Sado. This analysis showed that 83.3% of hip-fracture patients had past fracture. These data in other areas were obtained by interview, and indicated that 16.7–20.5% of hip-fracture patients had past fractures (Table 4). The percentage of patients with past fracture among spine-fracture patients ranged from 12.9 to 25.0%. Past spine-compression fracture was most common in both hip and spine-fracture patients. Because the data range was wide and there was a large difference between the fractures counted by interview and those assessed by X-ray, including asymptomatic

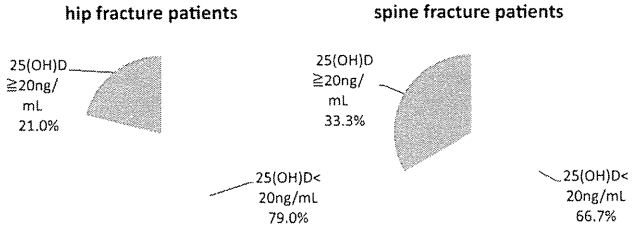

Fig. 1 Percentages of patients with hip or spine fracture with high and low serum 25-OHD levels. The percentages of patients with 25(OH)D < 20 ng/mL were 79.0% in hip-fracture cases and 66.7% in spine-fracture cases

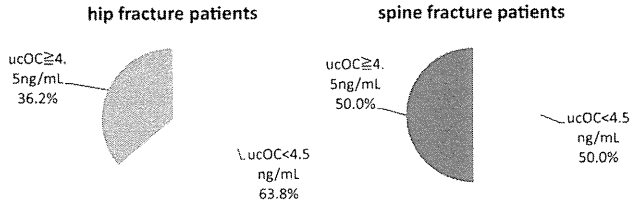

Fig. 2 Percentages of patients with hip or spine fracture with high and low serum ucOC levels. The percentages of patients with ucOC ≥ 4.5 ng/mL were 36.2% in hip-fracture cases and 50.0% in spine-fracture cases

Table 4 Numbers of patients who had past fracture

Area	Patients with hip fracture *N* (%)	Patients with spine fracture *N* (%)
Sado	55[a] (83.3)	4 (12.9)
Aichi	8 (16.7)	5 (25.0)
Tottori	7 (18.4)	3 (21.4)
Kumamoto	15 (20.5)	–

N, number of patients who had past fractures (spine, hip, distal radius, and proximal humerus)

[a] Asymptomatic past spine-compression fracture was assessed by X-ray in Sado. Other data were obtained by interview

compression fracture, we concluded that accurate information on past fractures cannot be obtained by interview.

Discussion

Serum 25 (OH)D and ucOC status

The serum 25(OH)D was low in both hip and spine-fracture patients in all four areas (<20 ng/mL). Intact PTH was slightly elevated in both fracture types and all areas. Low 25(OH)D (vitamin D insufficiency) leads to a high level of intact PTH, indicating slight secondary hyperparathyroidism.

Serum 25(OH)D differences caused by changes in daylight hours at different latitudes are thought to affect the incidence of hip fracture, but this study showed no marked regional differences for either fracture type. However, because data from Northern Japan were not included in this study, it is unclear whether there is any regional difference in an area of higher latitude than Sado.

Fewer fermented soybeans (Natto) are consumed in Western Japan than in the Eastern part of the country [21], and ucOC levels can be viewed in this context. However, there were no significant regional differences in these levels in this study.

Comparison of hip and spine fracture

We also examined differences between hip and spine fractures. The average age at the time of injury was 2.4 years older for hip-fracture cases than for spine-fracture cases ($P < 0.01$). Because approximately 80% of patients with hip fracture also have spine fracture [5], this suggests a chain of events of vitamin D insufficiency → bone absorption acceleration → spine fracture → hip fracture.

The 25(OH)D level was lower ($P < 0.05$) and intact PTH tended to be higher (N.S.) in hip-fracture patients than in spine-fracture patients (Table 3). Low 25(OH)D was more common in hip fracture, and almost two-thirds of spine-fracture patients also had low 25(OH)D (Fig. 1). These results indicate that vitamin D insufficiency and resulting slight hyperparathyroidism were present in patients with both kinds of fracture. These conditions were more severe in hip-fracture patients, which is consistent with the chain of events described above.

The ucOC level was higher in spine fracture than in hip fracture ($P < 0.01$) (Table 3). High ucOC was found in half of the spine-fracture patients, but only one-third of the hip-fracture patients (Fig. 2). That is, vitamin K deficiency was more serious in spine-fracture patients than in hip-fracture patients. However, other factors tended to be more severe in hip-fracture patients. This contradictory result might be because of a change in the serum ucOC level in the period after fracture and before measurement. Blood samples may not always have been collected within 1 week after fracture in spine-fracture cases, because it was not always clear when the fracture had occurred. Therefore, we cannot exclude the possibility of a change in the serum ucOC level in the period after fracture.

Tsugawa et al. [22] reported that the incidence of vertebral fracture in patients with a low plasma phylloquinone (K_1) concentration was significantly higher than that in those with a high K_1 level. However, the ucOC level has not been compared between cases of hip and spine fracture, and clarification of this issue requires further study.

This study was performed in several areas across Japan. The results indicated that differences between hip and

spine fracture were more significant than regional differences. We note that our data do not cover the entire country and further studies of regional differences are required. However, there are few spine-fracture cases in some regions and values for BMD and ucOC are not available in some areas, which may prevent complete analysis. Within this limitation, our results show that both hip and spine-fracture patients have vitamin D insufficiency, which is a risk factor for fracture, based on measurement of serum 25(OH)D and other factors in elderly patients in four areas of Japan. The severity of this condition was more serious in hip-fracture patients.

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