表2 杏林大学病院もの忘れセンター通院中の患者における老年症候群の頻度

| 老年症候群 | 頻度(%) |
|---|---|
| つまずき | 32.1 |
| 便 秘 | 26.3 |
| 歩行障害 | 23.2 |
| 頻 尿 | 22.1 |
| 不 眠 | 18.9 |
| めまい | 18.9 |
| 転 倒 | 17.9 |
| しびれ | 16.6 |
| 食欲低下 | 14.7 |
| 嚥下障害 | 14.7 |
| 体重減少 | 14.2 |
| 尿失禁 | 13.8 |
| 妄 想 | 9.5 |
| 無気力 | 7.6 |
| 幻 覚 | 6.8 |
| 振 戦 | 5.3 |
| 筋固縮 | 3.2 |
| 言語障害 | 2.7 |

が望ましい(**表1**). 一方，中期以降は記憶障害が強くなるとともに，判断力の低下や見当識障害，失認，失行など日常生活に具体的な影響が出てくる．このような認知障害に直接起因する中核症状に加えて，周辺症状が出現しやすいのもこの時期である．周辺症状とは，患者を取り巻く環境や身体上の問題を自分で適切に処理することができないために起こる反応性の行動異常で，不安，焦燥，興奮，妄想，不眠，不穏，幻覚，徘徊などがある．これらの症状はしばしば同居する介護者を悩ませる．したがって，中期以降は家族だけでなく地域(地域包括支援センターなど)と連携して，ケアマネージャーと相談しながら患者をサポートしていく必要がある．特に徘徊がみられる患者に対しては，地域ぐるみの理解，対応が必要である．周辺症状が著しい場合には，漢方薬や抗精神病薬などの薬物療法を行うこともある．

認知症中期には様々なADLの障害も現れる．ADLの病期の評価には手段的ADLや基本的ADL(**表3**)，Functional Assessment Staging (FAST)(**表4**)が使用しやすく，適している．そのほか認知症高齢者では，介護保険申請のための主治医意見書に用いられる'認知症高齢者のための日常生活自立度'は身近な評価尺度である．日常生活自立度判定基準の内容には，手段的ADL(買物，金銭管理，服薬管理，電話の応対)や基本的ADL(着替え，入浴，食事，排便，排尿)の要素が加わっている．手段的ADLに障害があればランクII，基本的ADLに障害があればランクIIIと考えればよい．

表3 ADLの評価方法
(文献[1,2]より引用)

| 手段的ADL | 基本的ADL |
|---|---|
| 電話の使用 | ベッドからの移動 |
| 買物 | 歩行 |
| 食事の準備 | 整容 |
| 家事 | 更衣 |
| 洗濯 | トイレ動作 |
| 乗り物を使った移動 | 排尿 |
| 服薬管理 | 排便 |
| お金の管理 | 食事 |
| | 階段昇降 |
| | 入浴 |

ADLの障害が強くなるほど，また，周辺症状の出現とともに，身辺のケアなど生活介護の比重が増大する．これに伴い，訪問介護の導入，デイサービス，デイケアの利用など，介護サポートが必要になる．

## 4. 認知症後期の老年症候群

認知症後期には失見当識，失認，失行が進行し，トイレ動作がうまくできず，オムツを使用することが多い．また，コミュニケーション障害，特に言語障害もみられるようになる．更に，食事に対する意欲がなくなり，低栄養状態に陥りやすい．低栄養は筋力の低下につながり，廃用を進め臥床時間が長くなる．低栄養状態で臥床時間が長くなると褥瘡ができる．このようにして認知症高齢者は多くの老年症候群(廃用症候群)を合併する．嚥下障害があり経口摂取が困難になると，経鼻胃管や胃瘻につながる．こうした患者は誤嚥を起こしやすく，しばしば肺

**表4 FAST(Functional Assessment Staging)**(文献[3]より引用)

日常生活動作能力を総合的に評価し，アルツハイマー型認知症(AD)の重症度を判定する．家族・本人に確認しながら情報を聴取する．

ステージ1　認知機能の障害なし．(臨床診断：正常)
主観的および客観的機能低下は認められない．

ステージ2　非常に軽度の認知機能の低下．(臨床診断：年齢相応)
物の置き忘れを訴える．喚語困難．
物忘れは年齢相応の変化．
多くの場合，正常な老化以外の状態は認められない．

ステージ3　軽度の認知機能の低下．(臨床診断：境界状態)
熟練を要する仕事の場面では機能低下が同僚によって認められる．
新しい場所に旅行することは困難．
重要な約束を忘れてしまうことがある．臨床的には軽微である．

＜境界線＞

ステージ4　中等度の認知機能の低下．(臨床診断：軽度のAD)
夕食に客を招く段取りをつけたり，家計を管理したり，買い物をしたりする程度の仕事でも支障をきたす．
誰かがついていないと買い物の勘定ができない．
日常生活では介助を要しないが，社会生活では支障をきたす．

ステージ5　やや重度の認知機能の低下．(臨床診断：中等度のAD)
介助なしでは適切な洋服を選んで着ることができない．
入浴させるときに何とかなだめて説得することが必要．
家庭での日常生活ができない．
買い物を1人ですることができない．
毎日の入浴を忘れることがある．
無事故だった人が初めて事故を起こす．

＜中期＞⇒見当識障害，徘徊，家事ができない，入浴ができなくなる．

ステージ6　重度の認知機能の低下．(臨床診断：やや重度のAD)
・不適切な着衣
・入浴に介助を要する，入浴を嫌がる
・トイレの水を流せなくなる
・尿失禁
・便失禁

ステージ7　非常に重度の認知機能の低下．(臨床診断：重度のAD)
・最大限約6語に限定された言語能力低下
・理解しうる語彙は，ただ1つの単語となる
・歩行能力の喪失
・着座能力の喪失
・笑う能力の喪失
・昏迷，昏睡

＜後期-末期＞⇒疎通性の低下，食事に集中できない，排尿の失敗，放尿，失便
寝たきりが続き，上下肢の関節拘縮，嚥下障害

炎を起こす．このように終末期ともいえる認知症患者では介護の必要性もさることながら，医療の必要度が高くなる．

## 5. 高齢者総合機能評価

ここまで記したように，認知症は大脳の疾患であるが，実際に問題になるのは生活機能である．その意味では，認知症のある高齢者を診る

**表5　認知症高齢者を診るうえで知っておきたいこと（高齢者総合機能評価）**

- 手段的ADL，基本的ADLに関する具体的な状況
- 同居者は？　主たる介護者は？　介護の状況
- 介護保険の利用状況
- 日常生活の状況，外出の頻度，その様子
- 合併疾患は？　服用薬は？
- 老年症候群
- 認知機能
- 周辺症状の有無
- うつ状態→GDS15
  周囲の人（介護者，家族）との人間関係は？
- 意欲→vitality index（リハビリ，活動への積極性）
- 経済状況

うえで**表5**のような事項を評価することが望ましい．このうち，ADLや老年症候群，周辺症状については，これまで記載したとおりである．これ以外で重要なのは，同居者や主たる介護者が誰か，具体的な介護の状況，介護保険の有無，介護サービスの利用状況であろう．高齢者，特に認知症がある場合，サービスを導入しようとしても，うつや意欲の低下があり，うまくいかない場合も多い．うつや意欲の低下を評価する方法が，老年期うつ病尺度（GDS15）（**表6**）や生活意欲の指標（vitality index）（**表7**）である．

以上のように，認知症高齢者を診るためには，認知機能以外に生活機能まで多面的に評価し，具体策を講じることが重要である．これを実践するうえで，介護，福祉，看護など多職種と情報連携する必要がある．そしてこれを可能にするのが高齢者総合機能評価である．

## おわりに

認知症患者を診るためには総合機能評価を行い，ADLをはじめとして生活の様子を把握すること，また，ADLの低下につながる老年症候群をチェックすることが大切である．老年症候群の中でも頻度が高く，要介護につながりやすい，歩行障害・転倒，失禁，摂食・嚥下障害・低栄養には特に注意が必要である．各老年症候群の内容と対策については，他稿を参照されたい．

## 文　献

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表6 Geriatric Depression Scale(GDS)簡易版の日本語訳(文献[4]より引用)

| | 項目 | 1 0 | 1が0を記入 |
|---|---|---|---|
| 1 | 毎日の生活に満足していますか | いいえ はい | |
| 2 | 毎日の活動力や周囲に対する興味が低下したと思いますか | はい いいえ | |
| 3 | 生活が空虚だと思いますか | はい いいえ | |
| 4 | 毎日が退屈だと思うことが多いですか | はい いいえ | |
| 5 | 大抵は機嫌良く過ごすことが多いですか | いいえ はい | |
| 6 | 将来の漠然とした不安に駆られることが多いですか | はい いいえ | |
| 7 | 多くの場合は自分が幸福だと思いますか | いいえ はい | |
| 8 | 自分が無力だなあと思うことが多いですか | はい いいえ | |
| 9 | 外出したり何か新しいことをするよりも家にいたいと思いますか | はい いいえ | |
| 10 | なによりもまず，物忘れが気になりますか | はい いいえ | |
| 11 | いま生きていることが素晴らしいと思いますか | いいえ はい | |
| 12 | 生きていても仕方がないと思う気持ちになることがありますか | はい いいえ | |
| 13 | 自分が活気にあふれていると思いますか | いいえ はい | |
| 14 | 希望がないと思うことがありますか | はい いいえ | |
| 15 | 周りの人があなたより幸せそうに見えますか | はい いいえ | |

1，5，7，11，13には‘はい’に0点，‘いいえ’に1点を，2，3，4，6，8，9，10，12，14，15にはその逆を配点し合計する．5点以上がうつ傾向，10点以上がうつ状態とされている．

**表7 生活意欲の指標（vitality index）**（文献[5]より引用）

| | |
|---|---|
| 1）起床（wake up） | |
| いつも定時に起床している | 2 |
| 起こさないと起床しないことがある | 1 |
| 自分から起床することがない | 0 |
| 2）意志疎通（communication） | |
| 自分から挨拶する，話しかける | 2 |
| 挨拶，呼びかけに対し返答や笑顔がみられる | 1 |
| 反応がない | 0 |
| 3）食事（feeding） | |
| 自分で進んで食べようとする | 2 |
| 促されると食べようとする | 1 |
| 食事に関心がない，全く食べようとしない | 0 |
| 4）排泄（on and off toilet） | |
| いつも自ら便意尿意を伝える，あるいは自分で排便，排尿を行う | 2 |
| 時々尿意，便意を伝える | 1 |
| 排泄に全く関心がない | 0 |
| 5）リハビリ，活動（rehabilitation，activity） | |
| 自らリハビリに向かう，活動を求める | 2 |
| 促されて向かう | 1 |
| 拒否，無関心 | 0 |

除外規定：意識障害，高度の臓器障害，急性疾患（肺炎など発熱）

判定上の注意

1）薬剤の影響（睡眠薬など）を除外．起座できない場合，開眼し覚醒していれば2点
2）失語の合併がある場合，言語以外の表現でよい
3）器質的消化器疾患を除外．麻痺で食事の介護が必要な場合，介助により摂取意欲があれば2点（口まで運んでやった場合も積極的に食べようとすれば2点）
4）失禁の有無は問わない．尿意不明の場合，失禁後にいつも不快を伝えれば2点．
5）リハビリでなくとも散歩やレクリエーション，テレビでもよい．寝たきりの場合，受動的理学運動に対する反応で判定する．

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

*Yasuhito Terabe, MD,[*] Atsushi Harada, MD, PhD,[†] Haruhiko Tokuda, MD, PhD,[‡] Hiroyasu Okuizumi, MD, PhD,[§‖] Masahiro Nagaya, MD, PhD,[#] and Hiroshi Shimokata, MD, PhD[§]*

**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.

From the Departments of [*]Orthopedic Surgery, [†]Advanced Medicine, [‡]Clinical Laboratory, [§]Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Obu City, Aichi, Japan; [‖]Mimaki Onsen Clinic, Tomi City, Nagano, Japan; and [#]Geriatric Health Services Facility, Luminous Obu, Obu City, Aichi, Japan.

Address correspondence to Yasuhito Terabe, Department of Orthopaedic Surgery, National Center for Geriatrics and Gerontology, Gengo 35, Morioka-cho, Obu, Aichi, Japan. E-mail: yst-trb@ncgg.go.jp

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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

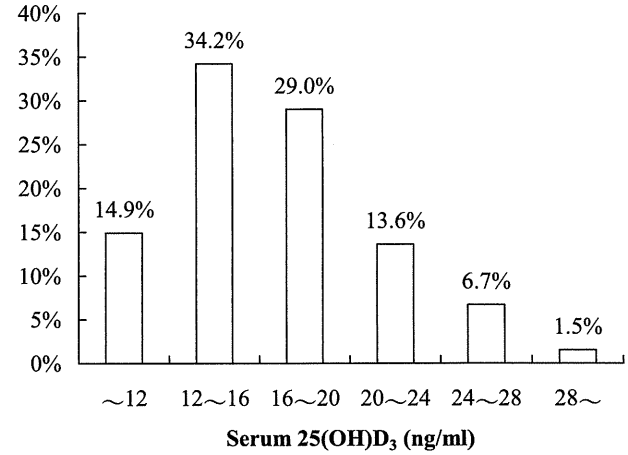


**Figure 1.** Percentile distribution of serum 25 hydroxy-vitamin $D_3$ (25(OH)$D_3$) concentrations. 25(OH)$D_3$ level was < 20 ng/mL in 78.1% and < 16 ng/mL in approximately half.

**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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**Conflict of Interest:** The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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**Author Contributions:** Yasuhito Terabe: Analysis and interpretation of data, preparation of manuscript. Atsushi Harada: Study concept and design, preparation of manuscript. Haruhiko Tokuda: Acquisition of data, preparation of manuscript. Hiroyasu Okuizumi: Acquisition of participants, preparation of manuscript. Masahiro Nagaya: Acquisition of participants and data, preparation of manuscript. Hirashi Shimokata: Analysis and interpretation of data.

**Sponsor's Role:** None.

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ORIGINAL ARTICLE

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

**Mayumi Sakuma · Naoto Endo · Hiroshi Hagino · Atsushi Harada · Yasumoto Matsui · Tetsuo Nakano · Kozo Nakamura**

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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.

N. Endo · H. Hagino · A. Harada · T. Nakano
Committee on Osteoporosis of the Japan Orthopedic Association, Tokyo, Japan

M. Sakuma
Department of Physical Therapy, Faculty of Medical Technology, Niigata University of Health and Welfare, Niigata, Japan

M. Sakuma (✉) · N. Endo
Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan
e-mail: m-sakuma@nuhw.ac.jp

A. Harada · Y. Matsui
Department of Advanced Medicine, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

H. Hagino
School of Health Science, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan

T. Nakano
Department of Orthopedic Surgery, Tamana Central Hospital, Kumamoto, Japan

K. Nakamura
Department of Orthopaedic Surgery, Sensory and Motor System Medicine, Surgical Sciences, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

## 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 ($kg/m^2$) | 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 ($kg/m^2$) | 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 ($g/cm^2$) | 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 $mg/cm^2$, $P < 0.001$).

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

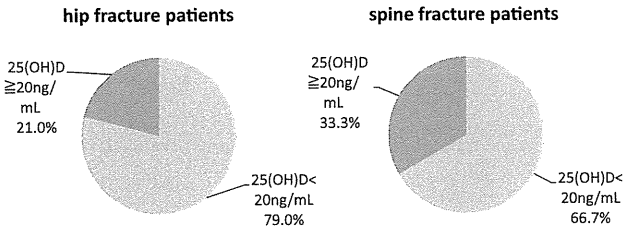


**Fig. 1** Percentages of patients with hip or spine fracture with high and low serum 25-OHD levels. The percentages of patients with 25(OH)D < 20 ng/mL were 79.0% in hip-fracture cases and 66.7% in spine-fracture cases

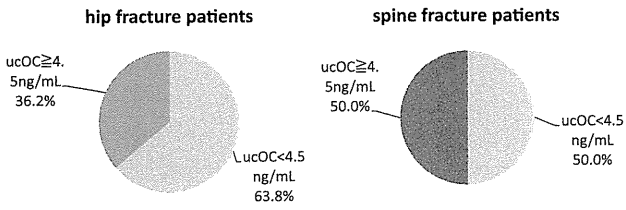


**Fig. 2** Percentages of patients with hip or spine fracture with high and low serum ucOC levels. The percentages of patients with ucOC ≥ 4.5 ng/mL were 36.2% in hip-fracture cases and 50.0% in spine-fracture cases

**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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COMPLICATION

# 男性更年期障害と筋肉減少症（サルコペニア）

国立長寿医療研究センター病院先端診療部部長 原田 敦
東京大学大学院医学系研究科加齢医学講座特任准教授 江頭 正人

## はじめに

女性では，閉経後の性ステロイドホルモンの急減がさまざまな更年期障害を起こすことはよく知られ，骨粗鬆症はその代表的疾患である。しかし，男性でも，精巣より分泌されるテストステロンの血中濃度は，成人以降加齢とともに緩徐に低下する。低下の程度には個人差が大きく，その程度が強くなった場合に男性更年期障害が出現するものと考えられる。脳を含む体中の臓器，組織，細胞にアンドロゲン受容体が存在し，テストステロンは性機能制御のほかに多くの未知の生理機能に関与していると考えられる。特に注目されるのが骨格筋作用で，培養骨格筋細胞でアンドロゲン受容体が発現し，テストステロンが筋芽細胞から骨格筋細胞への分化を促進すると報告されている[1]。

## 加齢男性性腺機能低下症候群（LOH症候群）と筋肉減少症

加齢に伴う男性の性腺機能低下症は，さまざまな名称を与えられていたが，2005年に加齢男性性腺機能低下症候群（late-onset hypogonadism syndrome：LOH症候群）と統一された。その定義は，“A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems”とされている[2]。これを受けた日本泌尿器科学会・日本Men's Health医学会「LOH症候群診療ガイドライン」検討ワーキング委員会によれば，LOH症候群の症候は表1[3]のごとくである。

診断は，遊離型テストステロン値が採用され，8.5pg/mLを正常下限値とした。さらに11.8pg/mL未満までをボーダーラインとするよう推奨されている。ボーダーライン例までにアンドロゲン補充療法が推奨されている。

ガイドラインには，筋量と筋力の低下が本症候群の主要症候の1つであることが記載されており，テストステロン欠乏の程度が重く，筋肉減少症（サルコペニア）の診断基準に該当するような男性も存在する可能性はあると思われる。

## サルコペニアの診断基準

2010年の欧州での合意によれば，サルコペニアの診断基準において，低筋量は必須項目で，それに低筋力あるいは低身体活動能が加わるとサルコペニアと診断される。診断アルゴリズムを図1に示す。筋量は二重エネルギーX線吸収測定法（dual-energy X-ray absorptiometry：DXA）や生体インピーダンス法で測定し，筋力は握力，身体活動性は歩行速度が採用されている。原発性と二次性に分類され，さらに二次性は身体活動性，疾患性，栄養性に分けられている[4]。

## テストステロン欠乏とサルコペニア

24～90歳の男性を対象とした横断研究で，血中遊離型テストステロン濃度がDXAで求めた筋量と筋力に関連があったと報告されている[5]。また，別の男性横断研究では，遊離型テストステロン濃度と歩行速度や総合的身体機能スコアとの間に有意な関連を認めた[6]など，血中テストステロン濃度と筋量や筋力が正の相関を呈することは，かなり一致して報告されており，男性ではテストステロン欠乏はサルコペニアに関連している可能性があると考えられるが，身体活動能の低下とは必ずしも明快な関連は示されていないようである。

## テストステロン補充によるサルコペニア治療

血中テストステロン濃度が低値で比較的健康な高齢男性でテストステロン補充効果を検討した無作為化対照試験によれば，テストステロン60mg/日またはプラセボを6ヵ月間投与した結果，筋量はテストステロン群で増加したが，握力や膝伸展力などの筋力とUp&Goテストなどの身体活動能は両群で改善はみられなかった[7]。

このように，多くの研究でテストステロン補充が筋量増加には有効であると示されているが，より重要な筋力や身体活動能低下の防止につながっていないのが大きな問題である。

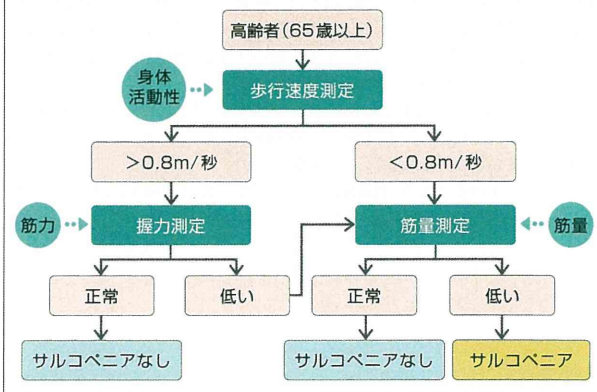
### ONE POINT ADVICE

女性だけでなく，男性においても，加齢とともに筋量低下と筋力あるいは身体活動能の低下がある程度以上に進むとサルコペニアとされる。テストステロン欠乏はサルコペニアに関連している可能性があると考えられ，男性でサルコペニアを疑う場合には，遊離型テストステロン濃度の低下と夜間睡眠時勃起の減退などで診断されるLOH症候群の合併も考慮する必要がある。

**表1. LOH症候群の症状および徴候[3]**

| |
|---|
| ①リビドー（性欲）と勃起能の質と頻度，とりわけ夜間睡眠時勃起の減退 |
| ②知的活動，認知力，見当識の低下および疲労感，抑うつ，短気などに伴う気分変調 |
| ③睡眠障害 |
| ④筋容量と筋力低下による除脂肪体重の減少 |
| ⑤内臓脂肪の増加 |
| ⑥体毛と皮膚の変化 |
| ⑦骨減少症と骨粗鬆症に伴う骨塩量の低下と骨折のリスク増加 |

**図1. サルコペニアの診断アルゴリズム**

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解説

# 高齢者の転倒と骨折
## -プロテクタの効用-

原田 敦*

# Prevention of Fractures from Falls in Elderly People
## - Effectiveness of Hip Protector -

Atsushi HARADA

Hip fracture usually occurs when the trochanteric region takes the impact of a fall. This confirmed in our experimental study, which showed that the fracture threshold for the hip of Japanese elderly was 2,166 N, while other researchers reported that the force exerted on the trochanter by a fall was 5,600 N. The large difference between these values explains the high incidence of hip fractures in the elderly. To prevent hip fractures, there are two major ways. First, the recent improvement of bone strength by osteoporosis medication has decreased the osteoporotic fracture risk by half. Second, hip protectors have significantly decreased the hip fracture risk in the frail elderly living at nursing homes.

**Key words**: Fall, Fracture, Prevention, Hip Protector, Osteoporosis

## 1. 緒 言

この 20 年近くを高齢者の人体損傷の代表である大腿骨近位部骨折の予防に費やしてきた．その間に骨強度と外力の両面から高齢者にも適応ができる介入法が実用化され，欧米では大腿骨近位部骨折頻度の減少が報告されるようになり，後期高齢者数がますます増加する状況の本邦でも本骨折の頻度上昇が一部の年代で止まったという報告がなされている[1]．

高齢期では骨折のほとんどの外力源が転倒である．従って，その予防には，骨強度と転倒外力の力学関係にかかっている．本稿ではそれに係る現状を臨床に携わる立場から報告する．

## 2. 転倒と骨折の現状

意図せずに地面や床，その他のより低いところに倒れることと定義される転倒[2]は，在宅高齢者の 1-2 割が毎年 1 回以上経験し，その 1 割が骨折を起こし，我が国の高齢者の要介護化の原因の 1 割を占める[3]．なかでも頻度と重篤度から最も影響が大きい大腿骨近位部骨折は，2007 年の全国調査では 14,8100 名に発生している[1]．

## 3. 骨強度と転倒外力

高齢者の骨強度を知るための大腿骨近位部破壊試験がいくつかある．いずれも外力を大転子外側に加えて転倒を模擬している．新鮮屍体骨を使用した試験では，大腿骨近位部が骨折する荷重は 2,100 N（平均 69 歳），3,400 N（平均 74 歳），4,000 N（平均 69 歳）と見積もられている[4-6]．我々の衝撃試験では保存大腿骨を用いたが，やはり 2,200 N（平均 73 歳）で骨折した[7]．これらは前期高齢期の結果であり、本骨折頻度が急上昇する後期高齢期女性ではさらに骨強度は低下すると想像される．

最近はCT有限要素モデル解析で骨強度を予測することが可能となり，我々が健常高齢者，転倒したが骨折しなかった患者，転倒して大腿骨近位部が骨折した患者の大腿骨近位部CT（骨折患者では健側）から予測した骨折荷重は，外側 0 度からの衝撃で，順に 1,893 N，1,706 N，1,472 Nであった。骨折者の骨強度は有意に健常者より低かった（Table 1）[8]．

転倒外力は，転倒様式で大きく変化し，一概に言えるようなものではないが，転倒による大転子部荷重が，若年ボランティアを水平位で 70 cmから落下させたときの荷重計測によれば，筋弛緩状態で 5,600 N，筋緊張状態で 8,600 N と予測されている[9]．もちろん若年データをそのまま高齢者に当てはめることはできないが，高齢者ではこのような試験は危険のため実施不可能であり，やはりシミュレーション方法をできる限り実際の高齢者条件に近づけて予測するしかないと考えられる．

## 4. 骨強度への介入による骨折予防

この 10 年で骨強度を改善して骨折を減らす骨粗鬆症治療薬が大きな成果を上げ，ビスフォスフォネートという薬剤を使用すれば，どの部位の骨折もほぼ半減させることができ，著者が取り組んできた大腿骨近位部骨折もその例外ではなく，臨床医のガイドラインにもその治療が最高ブレードのエビデンスとして推奨されている[3]．ただし，これらの薬剤は骨粗鬆症と診断された患者（骨量が若年成人平均値-2SDに該当する者）には前述した有効性が期待できるが，骨量が正常者にはその限りでなく，また，残り半分の骨折リスクが必ずしも下がらないことなど，骨粗鬆症治療薬だけでは限界も露呈された．課題は，骨強度を科学的に

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＊独立行政法人 国立長寿医療研究センター病院先端診療部
（〒474-8511 愛知県大府市森岡町源吾 35）

Table 1　Comparison of fracture load values (N) in the healthy, fragile and fracture groups differentiated by loading direction.

| Loading direction | Healthy group | Fragile group | Fracture group |
|---|---|---|---|
| -45 | 1423 | 1146 | 1126 |
| -30 | 1383 | 1216 | 1265 |
| -15 | 1546 | 1405 | 1356 |
| Zero | 1893 | 1706 | 1472* |
| 15 | 2022 | 1824 | 1522 |
| 30 | 1947 | 1728 | 1444** |

Multiple comparison with the healthy group by the Tukey-Kramermethod.　*: $p<0.05$, **: $p<0.01$

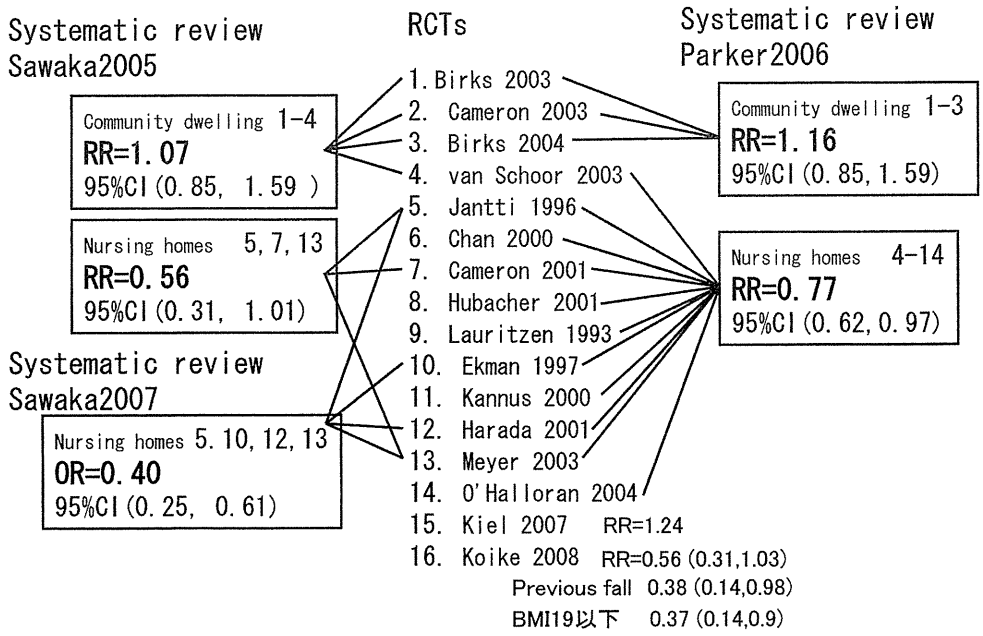


Fig.1　Systematic reviews of randomized controlled trials for hip protectors

いっそう正確に予測できるモデルの発展である．臨床では骨量と骨質で決定されると定義されているが，生体力学的に細胞分子レベルまで包含して種々の用途レベルに切り替えることが可能なものになれば，事故防止から薬剤医療機器開発や臨床試験に大きな力となると期待できる．

## 5．結　言

外力を減らす方策もこれまで長く実践されてきた．一つは転倒頻度を減少させるもので，「転倒予防」と呼ばれ，転倒リスクとなるバランス筋力の改善や関連薬剤調整，環境整備などで，転倒リスクを評価した上でそれに合った介入を行えば，80 歳以上の高齢者でも転倒頻度が減少するなどの高いグレードのエビデンスが明らかになった[10]．ただし，転倒頻度は減っても肝腎な骨折リスクの有意な低下は示されていない．

課題は，転倒様式の科学的解明である．人体損傷の危険度からみて，死に至る転倒，骨折に至る転倒，軽症で済む転倒，外傷なしの転倒と実に幅広い転倒条件に関する現場データ収集とモデル化が期待される．

一方，外力の大きさを減らす方法として，大腿骨近位部骨折に対するプロテクタが実用化され，転倒リスクの最も高い集団である介護施設高齢者ではこの骨折を減らすことが明らかとなった(Fig.1)[11]．我々の介護施設試験でもヒッププロテクターによって骨折リスクは大きく低下した[12]．ただし，この方法も転倒時に使用してなければ意味がなく，施設安全管理の観点から使用されてコンプライアンスが保てれば成果が上がるか，自主的な使用に頼る転倒リスクの低い在宅高齢者では無効であることも明らかとなり，いかに力学性能を上げてコンプライアンスも改善するかという課題は 10 年間抱えたままである．プロテクタ力学評価法の標準化は合意されている[13]．

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