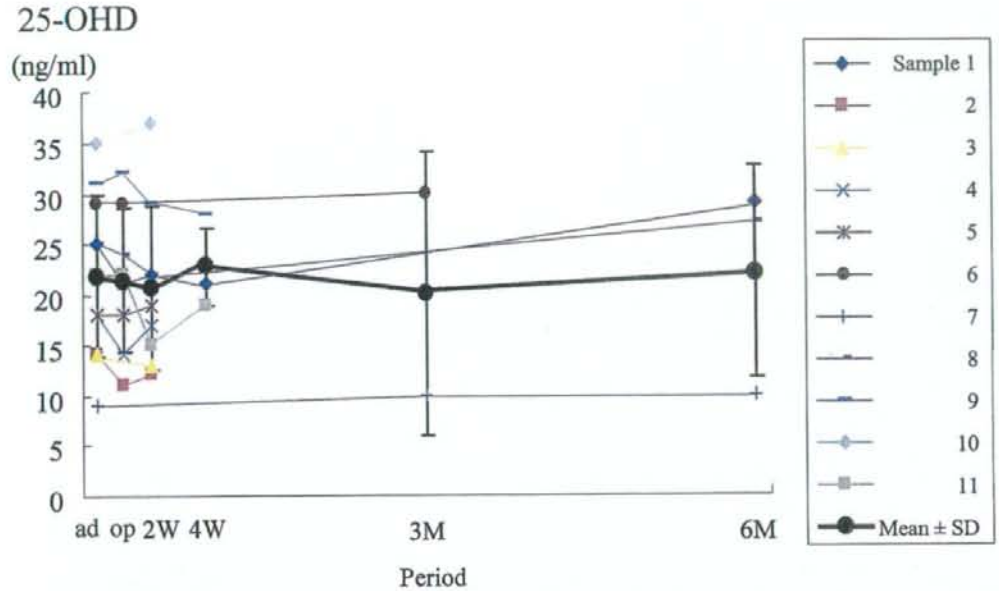

Fig. 1. Plots of the serum 25-hydroxycholecalciferol (25-OHD) level over time for all cases. The average maximum change from the mean value in each case was ± 8.5% (± 1.75 ng/mL).

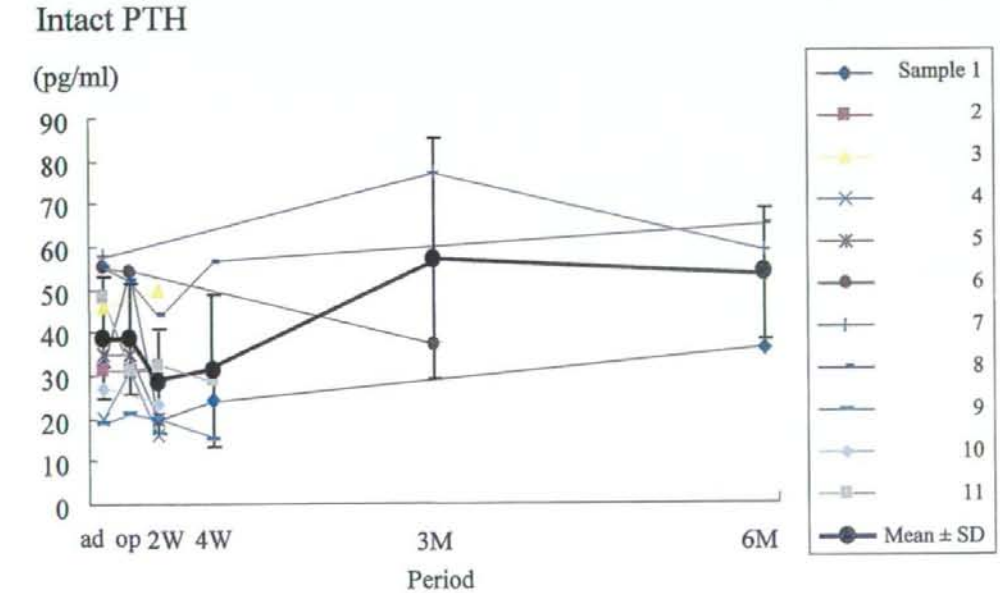

Fig. 2. Plots of the serum intact parathyroid hormone (PTH) level over time for all cases. The average maximum change from the mean value in each case was ± 20.7%.

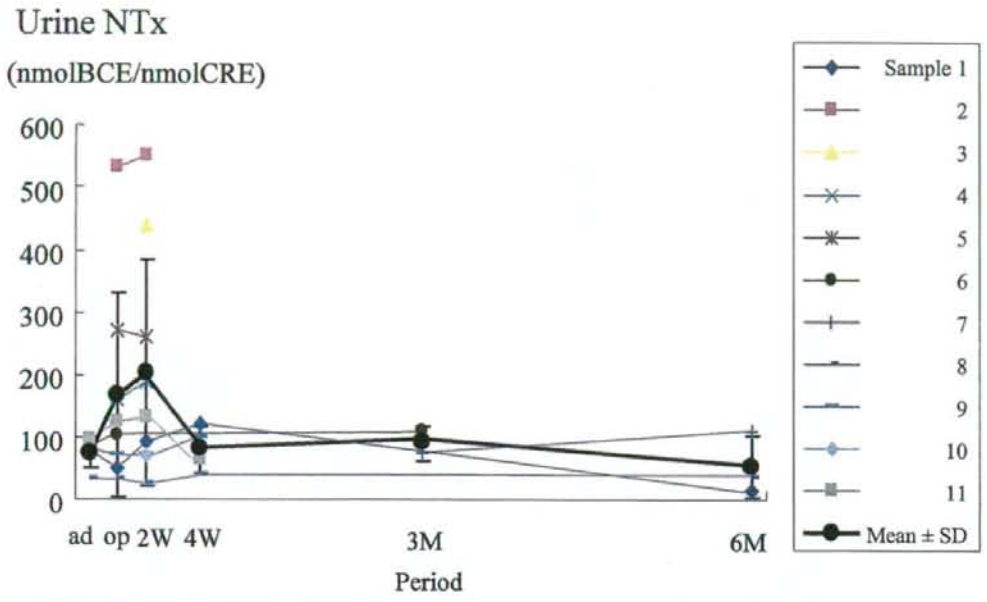

Fig. 3. Plots of the urine NTx level over time for all cases. The average maximum change from the mean value in each case was ± 19.4%.

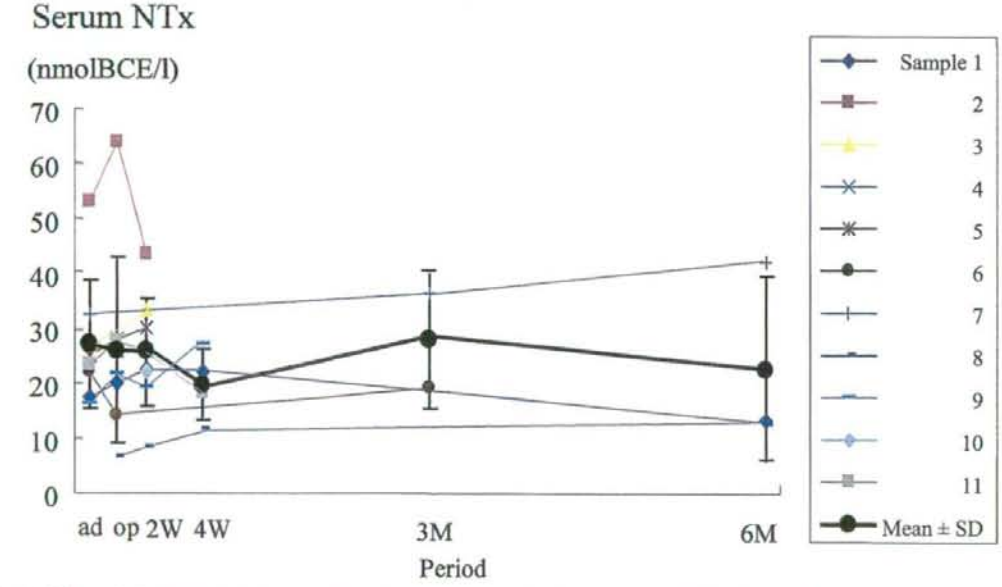

Fig. 4. Plots of the serum NTx level over time for all cases. The average maximum change from the mean value in each case was ± 18.0%.

Hormone assays

The 25-OHD level was measured by radioimmunoassay (RIA) using a kit supplied by DiaSorin (Stillwater, MN, USA), and intact PTH was measured by the chemiluminescence immunoassay (CLIA) method using a kit provided by Nichols Institute Diagnostics (San Clemente, CA, USA). Urine and serum levels of NTx were measured by enzyme-linked immunosorbent assay (ELISA), using the Osteomark kit (Inverness Medical Professional Diagnostics, Princeton, NJ, USA).

Statistical analysis

ANOVA followed by the Bonferroni/Dunn test was used to evaluate differences in the data, with P values less than 0.05 considered to be statistically significant. Analysis was performed using StatView for Windows software (version 5.0).

RESULTS

Subject characteristics

The characteristics of the 11 patients are shown in Table 1. On discharge from the hospital, six patients returned home after an average hospitalization period of 32 days, while three patients returned to the hospital or the nursing home at which they had lived before the fracture, and two patients who had lived at home before the fracture moved into a hospital or a nursing home. The BMD of the non-fractured hip was measured by DXA in nine of the 11 patients, and the average BMD was 0.582 ± 0.13 g/cm^2. The average serum total protein level was 6.53 ± 0.7 g/dl. Renal function and liver function, as determined by the serum creatinine level and by serum ALT and AST levels, respectively, were close to the normal ranges, and all patients had normal serum calcium and phosphorus.

The serum levels of 25-OHD are shown in Fig. 1. The average at the time of admission was 20.8 ng/mL (< 20 ng/mL in five of the 11 patients), and in most cases this level changed little in the six months after the fracture occurred: the average maximum change was ± 8.5% (± 1.75 ng/mL), and no significant difference was observed in comparison of serum 25-OHD levels for any pair of time points. The serum levels of intact PTH are shown in Fig. 2. Intact PTH was higher after three months than after two weeks or six months, and higher after six months than after two weeks: the average maximum change was ± 20.7%, but no significant difference was observed in comparison of serum PTH levels for any pair of time points. The urine and serum levels of NTx are shown in Figs 3 and 4, respectively. Urine NTx levels changed until four weeks after fracture, and individual differences were observed; there were, however, insufficient data for urine NTx after four weeks to perform any statistical analysis. The average maximum change in urine NTx was ± 19.4%, though no significant difference was observed in comparison of the urine NTx levels for any pair of time points. Serum NTx levels also increased for two weeks after fracture in six of 11 cases, though smaller changes in serum NTx were observed in comparison with urine NTx; the mean maximum change was ± 18.0%, and no significant difference was observed between data for any pair of time points.

DISCUSSION

The serum levels of 25-OHD showed little change in osteoporotic patients. Tauber et al.[7] found that the blood level of 25-OHD$_3$ is reduced during fracture repair in humans and suggested that this could be related to reduced outdoor activity; however, these results were obtained in patients undergoing prolonged fracture healing. On the other hand, Meller et al.[8] reported that PTH and 25-OHD$_3$ do not show significant changes during the healing period for fractures in young adults. Yu-Yahiro et al.[9] reported that intact PTH levels gradually rise after fracture and are significantly elevated after 365 days, compared with all other time points; however, their study also showed that intact PTH is somewhat decreased 10 days after fracture and returns to a baseline level after 60 days. In our subjects, the intact PTH level was higher three months after fracture than two-four weeks after fracture (not significant), an observation that is not contradictory with previous results. Ingle et al.[10] showed that urine NTx slightly increases following fracture and then decreases from 12 to 52 weeks. In the current study, numerical variation and the small sample size prevented these changes from reaching a statistical significance. Changes in serum NTx were also observed, but these were smaller than the changes in urine NTx. Overall, our data are consistent with previous studies, but the small sample size and lack of data for some variables at certain time points indicate that more detailed studies are needed to confirm these results.

CONCLUSION

The serum 25-OHD level did not change greatly after fracture, in comparison with the levels of intact PTH and NTx.

Acknowledgments. We are grateful to all the staff at Niigata Rinko General Hospital, for their advice and their technical support.

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血中ビタミンD低値と大腿骨頸部骨折

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ビタミンD不足は高齢者に多く見られ，特に骨折との関係が近年注目されている。このビタミンDの状態は，血清25 (OH) Dを測定することにより把握される。大腿骨頸部骨折患者の血清25 (OH) Dレベルは高率に低値であり，ビタミンD不足の状態が示されている。ビタミンD不足に適切に対応することが，骨折予防のための一つの可能性を示すものと期待される。最近の研究の結果を交え，ここではビタミンDの観点から骨折を考えたい。

The relationship between vitamin D insufficiency and hip fracture.

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Recently the relationship of vitamin D insufficiency and fracture is noticed in elderly people. Vitamin D nutritional status is evaluated by measuring serum 25 (OH) D. Higher prevalence of vitamin D insufficiency is observed in the patients with hip fracture. This suggests that vitamin D insufficiency is one of fracture risk factor and improvement of vitamin D status reduce fracture risk. With the results of recent studies, we would like to discuss about fractures from the viewpoint of vitamin D insufficiency.

はじめに

本邦における高齢者が寝たきりになる原因として，「骨折・転倒」は「脳血管疾患」に次ぐ主要な要因であり，特に，骨折においては大腿骨頸部骨折がその中核をなす重要な疾患であると言えよう。

高齢化の進む今日，健康で自立した生活を維

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持・増進することが求められている。すなわち，高齢となっても高い quality of life (QOL) を維持することは重要な課題である。大腿骨頸部骨折[用注]は，自立性を喪失，障害する疾患であることから，骨折を予防し危険因子に対応することは，QOLの向上につながると考えられる。

一方，ビタミンDは，特に高齢者における低栄養の観点から，さらに若年層においても過度のダイエットや偏食によるビタミンD不足が将来の骨粗鬆症予備群を生む可能性につながり，注目されている。また，骨折とビタミンD欠乏が関連するとのデータが徐々に集積されてきている。

ここでは，大腿骨頸部骨折と血清ビタミンDレベルについて述べたい。

ビタミンD代謝

ビタミンDは主に，D_2とD_3が自然界に多く分布し，高い生物効力を持つ。D_2はシイタケなどの植物性食品に含まれ，通常その量はD_3に比べわずかである。D_3は卵黄，牛乳，乳製品，魚類などの食物に含まれるが量としてはあまり多くなく，大半が皮膚などで生成する内因性のものに由来する。

日照により皮膚で生成したビタミンD_3，または経口的に摂取されたビタミンDは，肝臓で25位が水酸化されて25(OH)Dとなり，血漿中を循環する。これ自体には生理作用はないとされ，次に腎臓で1α位または24位が水酸化されて，1,25$(OH)_2$Dまたは24,25$(OH)_2$Dに代謝される。1,25$(OH)_2$Dは活性型ビタミンDとしてその効力を発揮し，小腸，腎のカルシウム(Ca)吸収を促進する。また，骨におけるCa代謝調整，副甲状腺におけるPTHの分泌調節にも関与する。

ビタミンDの供給レベルはより安定なかたちで血中を循環する血清25(OH)Dレベルから判断される。

ビタミンDの転倒，動揺性への影響

大腿骨頸部骨折の原因としては，転倒によるものがその大部分を占める。従って，骨強度のみならず，高齢者における易転倒性，動揺性，筋力低下などは骨折の大きな危険因子となる。

Pfeiferら[1]は閉経後女性237名について，血清25(OH)Dレベルが体幹動揺性と負の相関をすることを示した。Steinら[2]は，転倒経験の有無との関係を検討した結果，転倒経験者は非経験者に比べて血清25(OH)Dレベルが低値であると報告している。これらのメカニズムとして，ビタミンDが筋細胞や神経細胞のビタミンD受容体に作用して筋と神経の協調性を高め，重心動揺を減らす方向に働くのではないかとの機序が考えられている[1)~3)]。

高齢者の栄養とビタミンD

高齢者では腸管からのCa吸収能が低下し，腎におけるビタミンD活性化能が減弱し，二次的にPTHの分泌が亢進しているとされている。その観点から，ビタミンD，Caを補充することは有用である。

我が国の高齢者で，実際どのくらいビタミンDが不足しているのかについて近年研究成果が集まりつつある。Nakamuraら[4]は，日本人でビタミンDの摂取が少なく，魚を多く摂取する人でも不足していること，食事のみでは十分なビタミンD摂取が期待できないこと，さらには高齢者だけではなく若年層でも不足していることを報告している。岡野ら[5]の報告では，平均年齢65歳の女性462例において，血清25(OH)D_3が20ng/mL(ビタミンD不足)が55%，12.5ng/mL未満(ビタミンD欠乏)が5%にも認められた。特に80歳以上では，70%がビタミンD不足であったと報告している。

大腿骨頸部骨折：近位部すなわち頸部・転子部骨折を合わせた表現。ここでは以前より用いられている頸部骨折と称する。

表1　骨折群 vs 非骨折群の比較（年齢調整）

骨折群では非骨折群に比べ，25(OH)D，アルブミンが有意に低く，intact PTH が有意に高い。

測定項目	骨折群 (n = 30)	非骨折群 (n = 28)	p 値
年齢（歳）	67～88	70～87	−
年齢平均（歳）	79.9±5.4	77.5±4.8	ns
アルブミン（g/L）	3.6±0.5	4.0±0.5	< 0.05
ALP（IU/L）	309.0±281	255.3±112	ns
25（OH）D（ng/mL）	16.6±6.3	22.0±6.0	< 0.01
intact PTH（pg/mL）	45.8±20.4	35.8±22.8	< 0.05
残存歯牙数	6.3±8.9	8.9±9.5	ns

ALP：アルカリホスファターゼ，ns：有意差なし，PTH：副甲状腺ホルモン
（文献9より）

以上の報告は，少なくとも我が国ではビタミンD摂取量が不足しており，特に高齢者において高率に血清25(OH)Dが低値であることを示している。

血清ビタミンDレベルと大腿骨頸部骨折との関連～歯，認知機能，活動度を含めて～

そこで，実際の骨折症例におけるビタミンD状態と骨折との関連が注目される。米国やイタリアにおいて，それぞれ大腿骨頸部骨折症例におけるビタミンDレベル，骨代謝について検討した結果，大腿骨頸部骨折患者は高率に血清25(OH)Dレベルが低値であるとの報告がみられる[6][7]。

筆者らは，新潟県佐渡市（一島一市，総人口70,011人，高齢化率34%）において1年間の大腿骨頸部骨折症例を調査した結果，大腿骨頸部骨折症例の血清25(OH)Dレベルが，骨折を有しない同地域の方に比べて低値であることを報告した[8][9]。年齢を調整した比較においても，骨折群では非骨折群に比べ，25(OH)D，アルブミンが有意に低く，intact PTHが有意に高かった（表1）。また，骨折例では，25(OH)Dが低値であってもintact PTHが上昇していない例が多数存在した（図1）。この機序についてはまだ明確とはなっていないが，こうした25(OH)DとintactPTH，Ca代謝の関係・メカニズムがより明らかになれば，個々の患者に合ったよりきめ細かな骨折予防や治療が期待できるのではないだろうか。

同調査で，骨折患者において25(OH)Dと歯の関係を調べた結果，残存歯牙数と25(OH)Dに有意な正の相関（$\alpha = 0.20$，$p < 0.05$）を認めた。歯数は年齢による影響も勿論大きいが，一方で高齢者の口腔状態と栄養状態，特にCaやビタミンDの摂取状況が関係するとの報告もされている[10][11]。口腔機能の悪化が栄養状態の悪化につながる，または相互に作用するという図式が想定できる。

同調査において，介護保険主治医意見書の判定基準（1999年厚生省通達）を用い，25(OH)Dと術前の認知症自立度・日常生活自立度との関連について調べた。25(OH)Dと認知症自立度度との関係では，認知症の程度が重くなるにつれ25(OH)D濃度が低下する傾向がみられた（p < 0.05）（図2）。同様に，25(OH)Dと日常生活自立度との関係では，自立度が低下するにつれ25(OH)Dの値が低下する傾向がみられた（有意差なし：ns）（図3）。

これらの要因については明確ではないが，活動

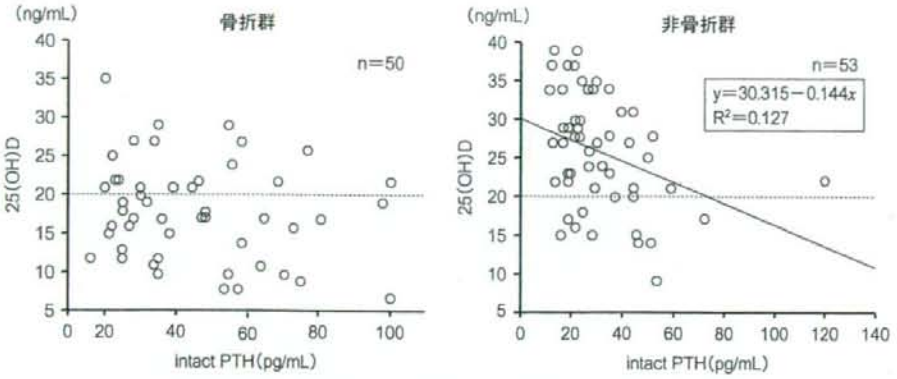

図1　25 (OH) D と intact PTH との関係

骨折群（左）では，62.0%（50 人中 31 人）が血清 25 (OH) D の値が 20ng/mL 以下であった。一方，対照群（右）では，血清 25 (OH) D が 20ng/mL 以下を示したのは 18.9%（53 人中 10 人）であった。
PTH：副甲状腺ホルモン
（文献 9 より）

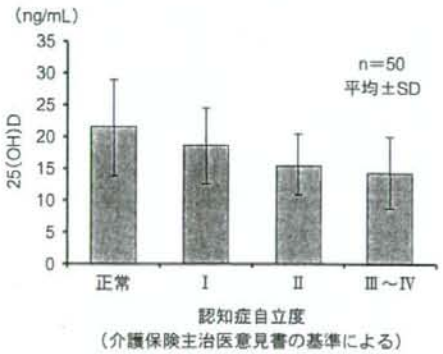

図2　大腿骨頸部骨折患者における認知症自立度と血清 25 (OH) D との関係

グラフの右側に行くに従い，認知症自立度が低下し，より重度な状態である。認知症が重くなるにつれ，血清 25 (OH) D の値が低下する傾向にある（$p < 0.05$）。
SD：標準偏差
（文献 9 より）

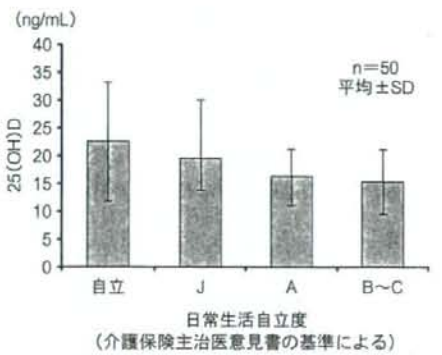

図3　大腿骨頸部骨折患者における日常生活自立度と血清 25 (OH) D との関係

グラフの右側に行くに従い，日常生活の自立度が低下した状態である。自立度が低下するにつれ，血清 25 (OH) D の値が低下する傾向にある（ns）。
ns：有意差なし，SD：標準偏差
（文献 9 より）

性の低下と 25 (OH) D の関係については日光曝露低下と皮膚におけるビタミンD産生の低下などの関与が考えられる。また，25 (OH) D と認知症については，アルツハイマー患者における 25 (OH) D の低値が報告されており[12]，認知症も含めて虚弱高齢者の潜在的なビタミンD不足が示唆される。

このように，大腿骨頸部骨折患者ではビタミンD不足が存在し，さらに口腔や栄養状態，認知機能，活動度とも関係していた。もちろんビタミン

D不足のみが原因ではないと思われるが，ビタミンD不足に対処し充足させることは，骨折予防や高齢者のQOL向上に対しさまざまな角度から有用である可能性が出てきた。今後もさらなる結果の集積が期待される。

おわりに

ビタミンD不足は高齢者で高率にみられ，骨粗鬆症，骨折の危険因子である。特に，25(OH)Dはビタミンドレベルを反映する指標として有用で，大腿骨頸部骨折症例では血清25(OH)Dが低値である。易転倒性，易骨折性，活動性や認知機能の問題，低栄養など，トータルで高齢者が抱えやすい問題に対し，潜在的なビタミンD不足が関与している可能性がある。もちろんビタミンD不足はこれらの諸問題に対する一要因として捉えられるべきであるが，骨折・転倒予防を中心としてさまざまな観点から検討の余地が見直されている。今後，このビタミンD不足蔓延という問題に現実的に対処していくことが，適切な治療・骨折予防への一つの糸口になるのではと考えている。

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ORIGINAL ARTICLE

Vitamin D and intact PTH status in patients with hip fracture

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Abstract
Introduction The prevalence of hypovitaminosis D in patients with acute hip fracture was examined in a population on Sado Island in Japan. There were 85 cases of hip fracture among this population in 2004, giving an overall incidence of hip fracture of 121.4 per 100,000 population per year. This study included 50 of the 85 cases, and these cases were defined as the hip fracture group. Patients older than 70 years without established osteoporosis who were admitted to the hospital on the island during almost the same period for treatment of an orthopedic condition other than a hip fracture were defined as the control group.
Materials and methods The levels of serum 25-hydroxyvitamin D (25-OHD), intact parathyroid hormone (intact PTH), alkaline phosphatase (ALP), albumin, and the number of remaining teeth were examined in each group. In the hip fracture group, serum calcium, serum phosphorus, urine N-terminal cross-linking telopeptide of type I collagen (NTx), bone mineral density (BMD) of the nonfractured hip, the presence of a vertebral fracture on X-ray, severity of dementia, and physical activity level were also examined.
Results Both the serum 25-OHD and serum albumin levels were significantly lower in patients with hip fracture than in controls, and the intact PTH level was significantly higher in patients with hip fracture. The number of remaining teeth was correlated with age, and was also significantly correlated with 25-OHD. In the hip fracture group, 62% of the subjects had hypovitaminosis D (25-OHD <20 ng/ml) and one-fifth of cases with hypovitaminosis D showed elevated PTH levels (>65 pg/ml). On the other hand, in the control group, hypovitaminosis D occurred in 18.9% of the subjects, and only one case showed elevated PTH. The serum 25-OHD level showed a decrease as the severity of dementia progressed and the activity level decreased.
Conclusion Our results indicate that about two-thirds (62%) of hip fracture patients had vitamin D insufficiency, suggesting that this condition may be closely associated with hip fracture in elderly people. Therefore, the serum 25-OHD level may be a useful index for the risk of hip fracture in elderly people.

Keywords 25-OHD · Activity · Dementia · Hip fracture · Intact PTH · Number of remaining teeth

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Introduction

The number of cases of hip fracture has been increasing with the aging of societies worldwide, and methods for the

prevention of hip fracture are therefore of value. Vitamin D is an important nutrient for bone health and is a regulator of calcium metabolism. Vitamin D deficiency leads to an increase in PTH levels, resulting in bone loss [1], and subclinical vitamin D deficiency is considered to be a risk factor for osteoporotic hip fracture in the elderly [2–4]. The aim of this study was to examine whether osteoporotic patients with hip fracture have lower levels of serum 25-hydroxyvitamin D (25-OHD) compared to non-osteoporotic cases, based on a study of the elderly population of a particular Japanese geographical area (Sado Island). The number of remaining teeth, dementia, and physical activity level were also examined in the study.

Patients and methods

Study site

This study was carried out on Sado Island, Japan. Sado Island is located in Niigata Prefecture in the Sea of Japan, at latitude 37°47′N to 38°20′N and longitude 138°12′E to 138°34E, situated north of the main Japanese island of Honshu. Sado Island has an area of 855 km^2 and the population of the island was 70,011 as of 30 June 2004, of which 23,787 (34%) were 65 years old and older. There were 1,754.5 h of daylight on the island during 2004. Tourism, fishing, and agriculture are the chief industries, and access to the island is only by ferry or airplane. Immigration and emigration among the elderly people of the island is extremely low.

Subjects

From January to December 2004, 85 patients (20 males and 65 females) visited the general hospital on Sado Island because of an acute hip fracture. All the patients lived on the island. Of the 85 patients, 81 (20 males and 61 females) were admitted to the hospital. Of these 81 patients, 2 were excluded from the study because they had a traumatic fracture, rather than an osteoporotic fracture. Patients with a generally poor medical condition and those who were immediately moved to another ward for treatment of an internal disease were also excluded from the study. After these exclusions, 50 remaining fracture patients (9 males and 41 females, 61–101 years old, average age: 82.6 years old) were included in the study. A control group was selected from patients who were admitted to the same general hospital with various orthopedic conditions from July to December 2004: 53 patients over 70 years old (25 males and 28 females, 70–96 years old, average age: 77.2 years old) with no clinical evidence of osteoporotic fractures were included in the control group. The patients (or their family if the patient had dementia) were informed of the nature of the study and consent was obtained from each participant.

Serum 25-OHD, intact parathyroid hormone (intact PTH), albumin, alkaline phosphatase (ALP), and the number of remaining teeth were checked at the time of admission. The number of remaining teeth was counted macroscopically by the examiner. Since a lack of teeth might be related to poor nutritional status and hypovitaminosis D, the relationship between the number of remaining teeth and the level of serum 25-OHD was also examined.

In patients with hip fracture, serum calcium, serum phosphorus, urine N-terminal cross-linking telopeptide of type I collagen (NTx), and the bone mineral density (BMD) of the nonfractured hip were measured, and the presence of vertebral fractures was determined by X-ray. In addition, the severity of dementia and the activity level before fracture were checked, using the criteria of the long-term care insurance system of the Japanese Ministry of Health, Labour and Welfare.

Serum, urine, and BMD measurements

Blood samples were collected at the time of admission. Serum calcium, serum phosphorus, serum albumin, and serum ALP were determined using standard methods. Serum calcium was adjusted for the albumin concentration [adjusted calcium (mg/dl) = calcium − albumin (g/dl) + 4.0] [5]. The serum creatinine, aspartate aminotransferase, and alanine aminotransferase levels were checked to examine liver and renal function. Intact PTH was measured by the chemiluminescence immunoassay (CLIA) method (Nichols Institute Diagnostics, San Clemente, CA, USA), in which intact PTH molecules are detected; the normal range is 10–65 pg/ml [6, 7]. We note that Segersten et al. [8] 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 serum 25-OHD level was measured by an enzyme-linked immunosorbent assay (ELISA) using a kit supplied by DiaSorin (Stillwater, MN, USA). A serum 25-OHD level of at least 15–20 ng/ml is needed to achieve optimum PTH levels, based on several reports. Hence, Hollis et al. [9] reported that the normal range of 25-OHD was 32–100 ng/ml and that a concentration of less than 10 ng/ml indicated a vitamin D-deficient state. Other studies performed in the US and Australia [10, 11] show that a serum 25-OHD level of at least 15–20 ng/ml is needed to achieve optimum PTH levels, and therefore we defined a 25-OHD level of less than 20 ng/ml as vitamin D

insufficiency. The value obtained at admission (from the day the fracture occurred until a few days later) was used as the serum 25-OHD level. The urine NTx assay was performed using the Osteomark NTx ELISA kit (Inverness Medical Professional Diagnostics, Princeton, NJ, USA).

BMD of the nonfractured hip was measured using a dual-energy X-ray absorptiometry (DXA) scan (Hologic 4500A, Bedford, MA, USA). The presence of vertebral fractures was also checked using the X-ray scan.

Severity of dementia and physical activity level

The severity of dementia was classified according to the criteria of the long-term care insurance system developed by the Japanese Ministry of Health, Labour and Welfare [12, 13], in which the severity of dementia is rated from I to IV, and M, as follows: I, some dementia, but independent in almost all daily activities in the community; II, symptoms and actions that impair daily activities or difficulty with mutual understanding, but independent with some attention; III, symptoms and actions that impair daily activities or difficulty with mutual understanding and requires care; IV, frequent symptoms and actions that impair daily activities or severe difficulty with mutual understanding and always require care; and M, a very severe case with extremely disruptive behavior, for which special medical care is required (in the current study no patients were in the M category). These standards were approved by the Japanese Ministry of Health, Labour and Welfare in 1993 [12, 13].

Physical activity level was also evaluated using the standards of the long-term care insurance system of Japan that are used to assess the degree of independence of disabled elderly people. These standards comprise four categories: J, some disabilities, but independent in activities of daily life; A, housebound, needing partial assistance only in outdoor activities; B, chairbound, needing partial assistance in indoor activities; and C, bedridden, dependent for most daily activities. These standards were approved by the Japanese Ministry of Health, Labour and Welfare in 1991 [12, 13] and are used generally in medical institutions in Japan.

The relationships of the serum 25-OHD level with the severity of dementia and the physical activity level were also determined.

Statistical analysis

Data are expressed as means±SD. Comparison between the two groups was performed using a Mann-Whitney U test, and correlations were examined using Spearman's rank correlation test. Regarding the dementia and activity level, a comparison among groups was performed using a Kruskal-Wallis test. Analysis was performed using StatView for Windows software (version 5.0).

Results

There were 85 cases of hip fracture on Sado Island in 2004, giving an overall incidence of 121.4 per 100,000 population per year. The male-to-female ratio was 1:3.25, and the cervical-to-trochanteric ratio was 1:1.30 (Table 1). Of the patients, 65.8% (25 of 38 cases) were classified as "osteoporotic" on the basis of WHO criteria, which defines osteoporosis as BMD below 2.5 standard deviations (SD) of the mean BMD for young adults [14]. Of the 85 patients, a group of 50 patients with hip fracture were judged eligible for the study and were compared with a group of 53 patients with other orthopedic diseases. All patients had normal renal function, based on a serum creatinine level within the normal range, and none of the patients had serum calcium and phosphorus levels consistent with a diagnosis of primary hyperparathyroidism or osteomalacia. The characteristics of the hip fracture patients are shown in Table 1. The average hip total BMD of the hip fracture group was 0.513 g/cm^2, and 81% of the patients had vertebral fractures (Table 1).

Table 1 Laboratory data for patients with hip fracture (n=50)

Variables	Male+female (n=50)	Male (n=9)	Female (n=41)
Serum calcium (mg/ml)	9.5±0.5	9.5±0.3	9.5±0.6
Serum phosphorus (mg/ml)	3.2±0.6	2.8±0.7	3.3±0.5
Urine NTx (nmol BCE/nmol Cr)	106.2±62.4	95.7±84.0	108.8±57.3
Hip BMD (g/cm^2)			
Total area	0.513±0.1	0.634±0.09	0.485±0.17
Neck	0.456±0.1	0.557±0.08	0.427±0.14
Trochanter	0.359±0.1	0.473±0.07	0.327±0.15
Intertrochanter	0.583±0.2	0.739±0.11	0.539±0.20
Ward's	0.218±0.1	0.270±0.88	0.203±0.13
Classified as osteoporotic on the basis of WHO criteria (%)[a]	65.8	57.1	67.7
Patients with vertebral fracture (%)[b]	81.8	62.5	86.1
Ratio of cervical to trochanter fractures	1:1.30	1:0.80	1:1.93

[a] Hip total BMD ≤−2.5: 38 patients were examined; 12 patients (2 males and 10 females) were not examined because there was no opportunity for a DXA examination

[b] 44 patients were examined; 6 patients (1 male and 5 females) were not examined because there was no opportunity for an X-ray examination

Table 2 Characteristics of patients in the study

Variables	Patients with hip fracture (n=50, 9 males and 41 females)	Non-hip fracture controls (n=53, 25 males and 28 females)	p value
Age range (years)	61–101	70–96	–
Average (years)	82.6±8.7	77.2±5.3	<0.01
Albumin (g/l)	3.53±0.5	3.97±0.5	<0.01
ALP (IU/l)	311.0±226	250.0±99.8	<0.05
25-OHD (ng/ml)	17.8±22.2	25.8±7.4	<0.01
Intact PTH (pg/ml)	45.1±22.2	31.4±18.3	<0.01
Number of remaining teeth	6.1±8.6	10.1±9.9	<0.05

Further characteristics of the patients in the study are shown in Table 2. Serum albumin levels were significantly lower (p<0.0001) in patients with hip fractures than in patients without hip fractures, and the hip fracture group had higher serum ALP levels, significantly lower serum 25-OHD levels (p<0.0001), and significantly higher intact PTH levels (p<0.001) compared to the control group. The number of remaining teeth in the hip fracture group was significantly fewer than in the control group (Table 2).

Because there was a significant difference in age and gender between the hip fracture group and the control group, a subgroup analysis was performed with adjustments for age and gender. There were 13 patients (2 males and 11 females) aged more than 90 years in the hip fracture group and there was 1 male only aged more than 90 years in the control group. There was no significant difference in age between the groups for subjects aged less than 90 years; therefore, a subgroup analysis was performed for women of less than 90 years of age in the hip fracture group (n=30, average age: 79.9 years old, range: 67–88 years old) and the control group (n=28, average age: 77.5 years old, range: 70–87 years old) (Table 3). Significant differences in albumin, 25-OHD, and intact PTH levels persisted in the subgroup analysis, but there was no significant difference in ALP level or in the number of teeth.

Correlations were also examined in the total population (n=103, 50 hip fracture patients and 53 controls) (Table 4): albumin was significantly inversely correlated with age (r=−0.22, p<0.05) and positively correlated with 25-OHD (r=0.35, p<0.05); 25-OHD was significantly inversely correlated with age (r=−0.24, p<0.05) and intact PTH (r=−0.40, p<0.01); and number of teeth was significantly inversely correlated with age (r=−0.45, p<0.01) and positively correlated with 25-OHD (r=0.20, p<0.05) (Table 4).

In hip fracture patients (n=50, 9 males and 41 females), intact PTH was significantly correlated with phosphorus (r=0.31, p<0.05) and NTx was significantly inversely correlated with 25-OHD (n=−0.44, p<0.01) (Table 5). In addition, BMD was significantly negatively correlated with age (r=−0.53, p<0.01) and NTx (r=−0.52, p<0.01), and number of teeth was significantly negatively correlated with age (r=−0.48, p<0.01) and BMD (r=−0.42, p<0.01). The relationships between intact PTH and 25-OHD level in patients with hip fracture (n=50) and in control subjects (n=53) are shown in Fig. 1. In the controls, there was a significant negative correlation between the intact PTH and 25-OHD levels (Fig. 1a, R^2=0.127), but this was not found in the hip fracture patients (Fig. 1b). In patients with hip fracture, 62.0% (31 of 50) had serum 25-OHD levels of less than 20 ng/ml, whereas in non-hip fracture patients, only 18.9% (10 of 53) had 25-OHD levels of less than 20 ng/ml.

Table 3 Sub-group analysis of women aged less than 90 years

Variables	Patients with hip fracture (n=30)	Non-hip fracture controls (n=28)	p value
Age range (years)	67–88	70–87	–
Average (years)	79.9±5.4	77.5±4.8	n.s.
Albumin (g/l)	3.6±0.5	4.0±0.5	<0.05
ALP (IU/l)	309.0±281	255.3±112	n.s.
25-OHD (ng/ml)	16.6±6.3	22.0±6.0	<0.01
Intact PTH (pg/ml)	45.8±20.4	35.8±22.8	<0.05
Number of remaining teeth	6.3±8.9	8.9±9.5	n.s.

Table 4 Correlation matrix for age, serum albumin, serum ALP, serum 25-OHD, serum intact PTH, and number of remaining teeth in the total population (fracture group and control group, n=103, 69 females and 34 males)

Variables	Albumin	ALP	25-OHD	Intact PTH	Number of remaining teeth
Age	−0.22*	0.10	−0.24*	0.19	−0.45**
Albumin	–	−0.11	0.35*	−0.06	0.18
ALP	–	–	−0.08	0.15	0.10
25-OHD	–	–	–	−0.40**	0.20*
Intact PTH	–	–	–	–	−0.17
Number of remaining teeth	–	–	–	–	–

*p<0.05; **p<0.01

Table 5 Correlation matrix for age, serum calcium, serum phosphorus, serum ALP, serum 25-OHD, serum intact PTH, urine NTx, BMD of the femoral neck, and number of teeth in patients with hip fracture (n=50, 9 males and females)

Variables	Calcium	Phosphorus	Albumin	ALP	25-OHD	Intact PTH	NTx	BMD	Number of teeth
Age	0.10	−0.10	−0.19	0.07	0.08	0.06	0.08	−0.53*	−0.48*
Calcium	–	0.10	−0.22	0.18	0.04	0.16	0.04	−028	−0.17
Phosphorus	–	–	0.06	−0.15	−0.05	0.31**	−0.10	0.11	−0.10
Albumin	–	–	–	−0.24	0.03	0.19	−0.31	0.18	0.04
ALP	–	–	–	–	0.01	0.18	0.14	0.02	0.19
25-OHD	–	–	–	–	–	−0.17	−0.44*	0.30	0.23
Intact PTH	–	–	–	–	–	–	−0.12	−0.04	−0.05
NTx	–	–	–	–	–	–	–	−0.52*	−0.03
BMD	–	–	–	–	–	–	–	–	−0.42*
Number of teeth	–	–	–	–	–	–	–	–	–

*p<0.01; **p<0.05

The hip fracture patients were also classified into two categories based on the level of 25-OHD: a hypovitaminosis group with 25-OHD <20 ng/ml and a normovitaminosis group with 25-OHD ≥20 ng/ml. NTx was significantly higher in patients with a lower level of 25-OHD (<20 ng/ml) (Table 6), but significant differences were not observed for other items in the 25-OHD subgroup analysis.

The relationship between dementia level and serum 25-OHD in the hip fracture patients (n=50) is shown in Fig. 2. The mean 25-OHD level was highest, at more than 20 ng/ml, in the normal (based on dementia level) group and then tended to decrease as the degree of dementia progressed (p<0.05). The relationship between physical activity level and serum 25-OHD in the hip fracture patients is shown in Fig. 3. The mean level of 25-OHD reached a level of more than 20 ng/ml in the group assessed to be independent and then tended to decrease as the degree of activity decreased.

Discussion

Our data show that the serum albumin level was significantly lower in the hip fracture group compared to the control group (Tables 2 and 3), consistent with the study of Thiebaud et al. [15], in which low albumin was also reported to be an important risk factor for hip fracture. The 25-OHD level was also significantly lower and the intact PTH level was significantly higher in the hip fracture group, also consistent with previously reported results [3, 4]. In the US, a serum 25-OHD level lower than 12 ng/ml was observed in 50% of women with osteoporotic hip fractures [4]. In Italy this value was found to be 13.5%, and 21.6% of patients had a serum 25-OHD level less than 20 ng/ml [3]. Our data show that 26% of the hip fracture patients (13 of 50) had a serum 25-OHD level of less than 12 ng/ml and 62% (31 of 50) had a level of less than 20 ng/ml; these percentages were higher than in the study performed in Italy, but lower than the study in the US. We note that intake of fishery products is very common on Sado Island, but despite these habits, vitamin D insufficiency was observed in patients with hip fracture. ALP was significantly higher

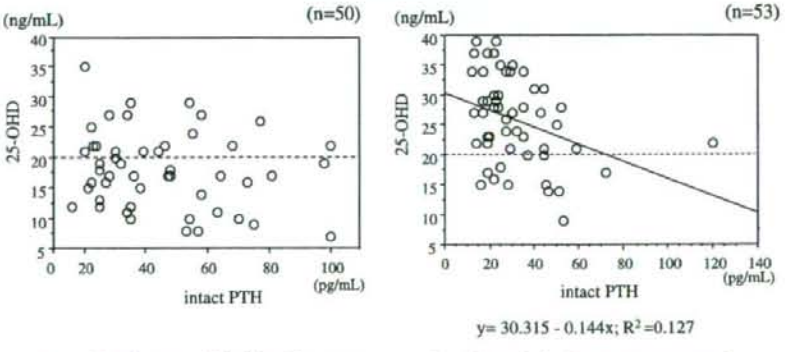

Fig. 1 Relationship between serum intact PTH and 25-OHD levels. **a** Patients with hip fracture. **b** Non-hip fracture controls. Of 50 patients with hip fracture, 31 (62.0%) had serum 25-OHD levels <20 ng/ml (**a**). Of 53 non-hip fracture controls, 10 (18.9%) had serum 25-OHD levels <20 ng/ml (**b**)

Table 6 Characteristics of patients with hip fracture grouped according to 25-OHD

Variables	25-OHD <20 ng/ml (n=31, 5 males and 26 females)	25-OHD ≥20 ng/ml (n=19, 4 males and females)	p value
Age range (years)	61–101	66–97	–
Average (years)	81.7±9.0	84.2±8.3	n.s.
Cervical-to-trochanter ratio	1:1.81	1:1.38	
Intact PTH (pg/ml)	46.7±22.6	42.5±21.7	n.s.
Calcium (mg/ml)	9.54±0.5	9.44±0.5	n.s.
Phosphorus (mg/ml)	3.30±0.5	3.05±0.7	n.s.
Albumin (g/l)	3.51±0.5	3.55±0.5	n.s.
ALP (IU/l)	320.0±278.4	296.4±100.9	n.s.
NTx (nmol BCE/nmol Cr)	117.6±60.7	84.3±61.9	<0.05
Number of remaining teeth	5.6±8.5	7.0±8.8	n.s.
Hip BMD (g/cm^2)			
Total area	0.490±0.171	0.551±0.164	n.s.
Neck	0.435±0.128	0.497±0.155	n.s.
Trochanter	0.344±0.166	0.381±0.129	n.s.
Intertrochanter	0.570±0.218	0.610±0.187	n.s.
Ward's	0.186±0.116	0.263±0.129	n.s.

and the number of teeth was significantly lower in the hip fracture group. However, since there were no significant differences in these items in a subgroup analysis in women less than 90 years old, the influence of age on ALP and number of teeth appeared to be significant.

Regarding the number of remaining teeth, there was no significant difference between the hip fracture group and the control group, but a strong correlation between age and the number of teeth was found. However, a significant correlation between 25-OHD and the number of teeth was

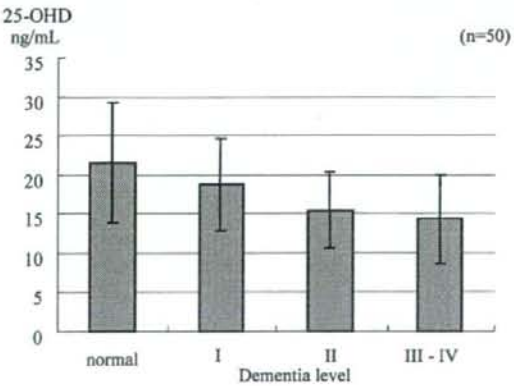

Fig. 2 Relationship between dementia level and 25-OHD in patients with hip fracture (p<0.05) (mean±SD)

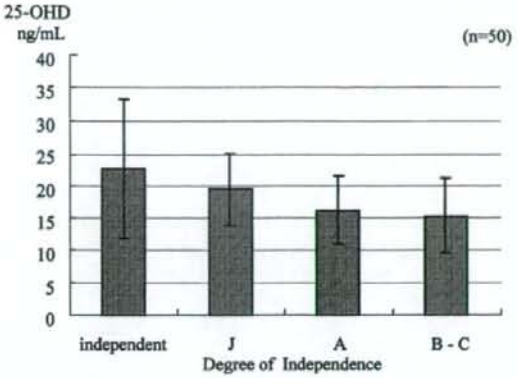

Fig. 3 Relationship between serum 25-OHD and degree of independence in patients with hip fracture (n.s.) (mean±SD)

also observed (Table 4). Bollen et al. [16] reported that the number of teeth is not influenced by fracture state, whereas Krall et al. [17] have suggested that intake levels of calcium and vitamin D have a beneficial effect on tooth retention. It appears likely that the number of remaining teeth is mainly influenced by age and is not necessarily associated with fracture directly, but may be associated with serum 25-OHD levels. The significant correlation between the number of teeth and BMD was mainly related to age (Table 5).

Regarding the relationship between intact PTH and 25-OHD levels, although intact PTH was significantly correlated with 25-OHD in the control group (r^2=0.127) (Fig. 1), no such correlation was found in the hip fracture group. When the 25-OHD level becomes insufficient, the intact PTH level generally rises. However, of the 31 patients in the current study with a low 25-OHD level, only a few (6 of 31) had an elevated PTH level (>65 pg/ml). Chapuy et al. [18] have reported that low serum 25-OHD does not always lead to an increase in serum PTH, and Sahota et al. [19] suggested that a slight reduction in serum calcium and a substantial decrease in 1,25-$(OH)_2$D levels may be partly related to the failure of the parathyroid gland to mount an adequate PTH response. In addition, the cutoff for definition of an elevated PTH level may require further examination.

The relationship of dementia level with 25-OHD indicated a tendency for the 25-OHD level to decrease as dementia progressed (Fig. 2). Sato et al. [20] reported that serum 25-OHD levels are significantly decreased in Alzheimer disease patients and that vitamin D deficiency due to sunlight deprivation and malnutrition contributes significantly to reduced BMD. The relationship of activity level with 25-OHD also indicated a tendency for the 25-OHD level to decrease as the activity level decreased (Fig. 3). Bishoff-Ferrari et al. [21] have reported that 25-OHD concentrations between 40 and

94 nmol/l are associated with better musculoskeletal function in the lower extremities, and Monaco et al. [22] reported a significant positive correlation between serum 25-OHD_3 and Barthel Index score in hip fracture patients.

Overall, our results suggest that dementia, decreased activity, and vitamin D deficiency are mutually associated and carry a high risk of hip fracture. In particular, of the patients with hip fracture in the current study, two-thirds had vitamin D deficiency. Since aging of the population is progressing and cases of hip fracture are likely to increase in number, we conclude that determination of the level of serum 25-OHD in elderly patients is of value, because vitamin D deficiency is a risk factor for hip fracture.

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REVIEW ARTICLE

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Features of limb fractures: a review of epidemiology from a Japanese perspective

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Key words epidemiology · fractures · osteoporosis · incidence · trends

Introduction

Fractures among the elderly which are associated with osteoporosis have become a major health and socioeconomic issue with the rapid increase in the elderly population in both Western and Asian countries. Among the elderly, bone mineral density (BMD) generally decreases with age, and the incidence of fractures increases with age, with the exception of the wrist (Fig. 1) [1]. Among adolescents, BMD increases with age, but the age-specific incidence of fractures does not decrease with age, but rather peaks at the time of the growth spurt (Fig. 1) [2]. These discrepancies between BMD and aging and fracture incidence seem to shed light on the pathogenesis and prevention of fractures.

In this review, the features of geriatric and adolescent limb fractures among the Japanese population will be presented, and an attempt will be made to identify factors for fracture prevention.

Fractures in adolescence

Incidence of fractures in adolescence

Fracture of the distal radius is the most common fracture among children, comprising 20% of total fractures under the age of 17 [3]. The age- and sex-specific incidences under 20 years of age were higher in males than in females, with peaks at 12 or 13 years for males and 11 years for females (Fig. 2) [2]. However, 13-year-old boys and 11-year-old girls are not more active or more prone to falls and trauma than children older or younger than 13 or 11. Therefore, the prominent peak in the incidence of fracture in adolescence has no relation to BMD or physical activity.

Bone mineral density and peak incidence

There is a close relationship between fracture incidence and the relatively low bone density of the radius. The age of peak incidence of distal radius fractures coincides with the age when the metaphyseal/diaphyseal density ratio is lowest (Fig. 2) [2]. The age at which the incidence of fractures peaks almost perfectly matches the age at which the speed of growth in height peaks in both boys and girls. This relative low bone density at the metaphysis is possibly caused by rapid growth during adolescence.

Rauch et al. [4] demonstrated that cortical thickness remains unchanged from 6 to 13 years in girls and from 6 to 15 years in boys, as measured by peripheral quantitative computed tomography (pQCT). The endocortical apposition rate at the distal radial metaphysis should be extremely high in order to maintain cortical thickness during growth. They estimated the endocortical apposition rate at the distal radius metaphysis to be about 9.5–10 μm/day, which is 10–20 times that of the periosteal apposition of the diaphysis. This makes it difficult for the bone to adapt its strength to the increased mechanical needs during growth [5]. After longitudinal growth ceases, the robustness of bone can catch up with the loading needs.

Recent trends

There has been some debate as to whether the incidence of fractures among children in Japan has increased or not. To address this question, all wrist fractures in Tottori Prefecture were surveyed from 1986 to 1995, and the age- and

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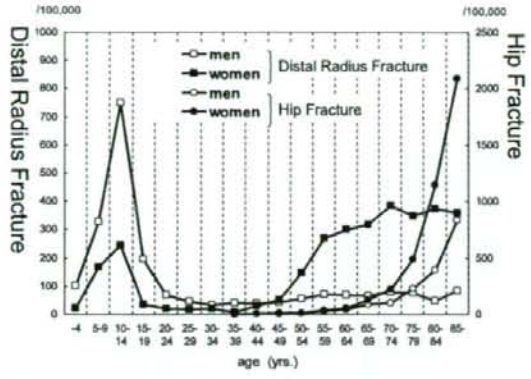

Fig. 1. Age- and sex-specific incidence rates of distal radius and hip fracture. Derived from data in Hagino et al. [1,2,7]

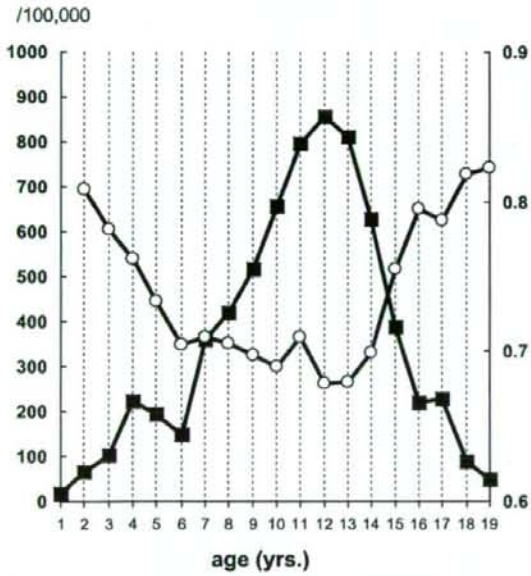

Fig. 2. Fracture incidence and BMD of the distal radial in adolescence for boys. Derived from data in Hagino et al. [2]. —■— Fracture incidence (lt. axis), —○— metaphyseal/diaphyseal density ratio (rt. axis)

sex-specific incidences were calculated, revealing that the incidence increased with time for males between 7 and 12 years of age [6]. Although the changes in incidence among females were not significant, the peak incidence increased during the observation period. Because the mean body height in Japanese adolescents is greater than was previously recognized, this may make the adaptation of bone to loading more difficult than before, and may contribute to weakness at the distal radius with time.

Table 1. Comparison of the incidence of hip fracture in various geographic areas

	Men	Women
Rochester, USA [9]	168.7	382.3
Central Finland [10]	147.8	290.7
Malmo, Sweden [11]	198.1	471.7
Picardy, France [12]	67.4	165.4
Cantabria, Spain [13]	54.2	205.5
Beijing, China [14]	53.3	59.4
Chonnam, Korea [15]	87.2	119.0
Tottori, Japan [7]	58.3	181.3

Data are incidences (per 100000 person-years) adjusted to the population structure of all of Japan (≧35 years, 2000)

Fractures in the elderly

Hip fracture

Lower incidence among the Asian population

There have been many epidemiological surveys of hip fractures all over the world. One of the conclusions derived from these studies is that hip fracture incidence is lower among Asian or African populations than among North American or northern European populations. The age- and sex-specific incidence of hip fractures for both sexes increased exponentially with age after 70 years (Fig. 1) [7,8]. Table 1 shows a comparison of the incidence of hip fracture among different populations based on previous studies. The incidences for both sexes in Asian populations, including Japanese, are substantially lower than those in Caucasian populations living in northern Europe or North America, but not in those in southern Europe.

As bone mass in Asians is known to be lower than or similar to that in Caucasians, the difference in bone mass does not explain the difference in the incidence of hip fractures [16]. Elucidation of the cause of the ethnic differences in the incidence of hip fracture may suggest preventive measures that could protect against osteoporosis-related fractures. Therefore, several different approaches have been tried in order to clarify why the incidence of hip fracture is lower in Asian populations.

Geometry of the proximal femur and fracture type

In the early 1990s, Yoshikawa et al. [17] and Nakamura et al. [18] found that the geometric characteristics of the proximal femoral neck in Japanese women are associated with a lower risk of hip fracture. Faulkner et al. [19] found that a hip axis length (HAL) of 11.0 cm corresponds to a doubling of hip fracture risk compared to women with a normal hip length. Duboeuf et al. [20] demonstrated that in the neck fracture group, the HAL was significantly longer than in controls, but this was not true in the trochanteric fracture group.

The incidence of trochanteric fracture is higher than that of neck fracture for individuals over 75 years of age (Fig. 3) [7]. The incidence of neck fracture is substantially lower

than that of trochanteric fractures in Japanese people, but this is not true for Caucasians. The incidence of neck fracture is higher than that of trochanteric fracture in northern European populations, and therefore the neck fracture/trochanteric fracture ratio is different in Japanese and northern Europeans (Fig. 4) [21,22]. The short HAL among Asians affects the lower incidence of neck fractures and might be one possible explanation for a lower incidence of hip fractures.

Risk factors

A case-control study in four Asian countries established the lifestyle factors associated with hip fracture; these are low dietary calcium intake, lack of regular load-bearing activity in the immediate past, no vigorous sports activity between 25 and 49 years of age, cigarette smoking (for men only), daily alcohol consumption, a history of fracture after 50 years of age, a history of falls in the year before a fracture, and a history of stroke [23]. Two studies have examined the risk factors for hip fracture among the Japanese population [24,25]. In one of these studies [23], Suzuki performed a case-control study and found that excessive coffee drinking and sleeping on a bed (as opposed to a futon) were significant risk factors.

In Japan, about 10%–20% of elderly people living in their own homes fall during a year, while 30%–40% fall in northern Europe and North America [26]. The fact that the prevalence of falls among Japanese is half that among Caucasians offers a possible explanation for the difference in the incidence of these fractures [27].

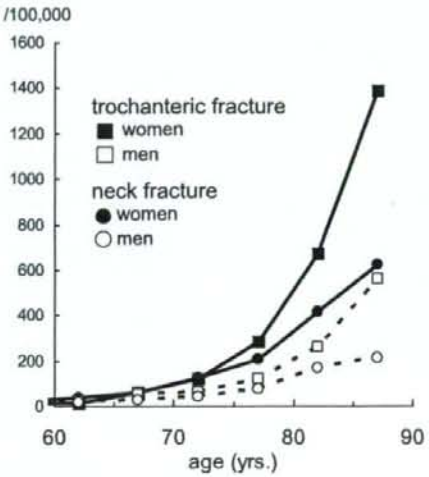

Fig. 3. Age-, sex-, and fracture-type-specific incidence rates of hip fracture in Tottori. Derived from data in Hagino et al. [7]

Changes in incidence over time

Recent trends in the incidence of hip fractures have varied between observation periods or geographic areas. Epidemiological surveys in Europe before 1990 showed that the incidence of hip fractures was increasing [11,28,29]. However, data from the 1990s or later from northern Europe [30,31], North America [32], and Australia [33] indicated that the increase had leveled off [34,35]. On the other hand, most reports from Asia indicate an increase in the incidence of hip fracture with time [7,8,36,37].

The reason for the discrepancies between races has not been clearly elucidated, although changes in lifestyle in Asian countries seem to affect the trend. In Singapore, hip fracture rates from 1991 to 1998 were 5 times higher than rates during the 1960s [38]. In Hong Kong, the fracture rates in 1995 for women 80 years and older were 3 times higher than corresponding rates in the 1960s [39]. However, the incidence rates in these two areas over the last decade have not changed appreciably. The increases were only 1.1 times in Singapore in the 1990s and 1.4 times in Hong Kong from 1985 to 1995. The increase in the incidence rate in Japan of 1.4 times from 1986 to 1998 was very similar. From these points of view, the age-specific incidence of hip fracture among developed and urbanized Asian areas seems to have leveled off over the last decade, even though increases still exist. Urbanization or industrialization, with attendant

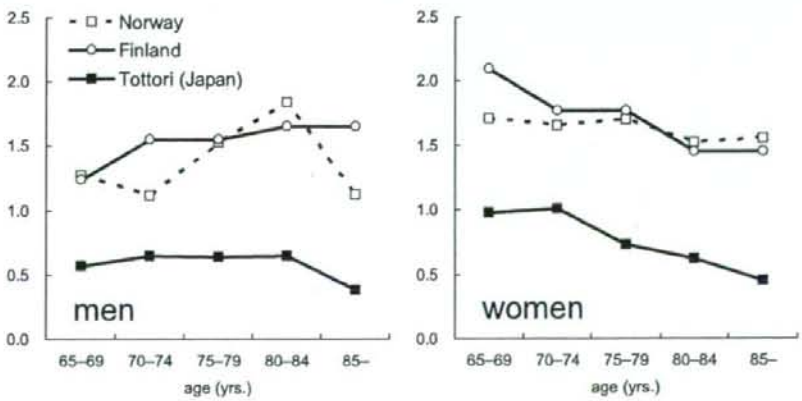

Fig. 4. Neck/trochanteric fracture ratio in different geographic areas. Derived from data in Bjorgul and Reikeras [21], Luthje et al. [22], and Hagino et al. [7]

changes in degree of physical activity, nutrition, alcohol intake, sedative drug use, and lifestyle in Asian countries, may contribute to the rising fracture trend by increasing bone fragility and the risk of falls. On the other hand, adequate diagnosis and treatment for osteoporosis is thought to relate to the decreased incidence of hip fracture in North America [35].

Upper limb fracture

Lower incidence among the Asian population

The incidence of wrist (distal radius) and proximal humerus fractures was surveyed in Tottori Prefecture (Fig. 1) [1]. In women, the incidence of wrist fractures increases after the menopause and plateaus at over 70 years of age; however, the incidence of proximal humerus fractures increases with age over 70 years. This is because elderly people over 75 have difficulty in protecting themselves with their hands when they fall, and instead they injure their hip or shoulder.

Although few epidemiological surveys have been performed to elucidate the incidence among Asian populations, the incidences of wrist and proximal humeral fractures are substantially lower among Japanese than Caucasians. Because 96% of wrist and 95% of humerus fractures are due to falls [40], the lower incidence of upper limb fractures seems to be closely related to the lower incidence of falls.

Risk factors

Epidemiological studies have indicated that risk factors for distal forearm fracture are low bone mass, estrogen deficiency, falls [41], and drinking alcohol [42, 43]. Poor visual acuity, frequent walking [44], and walking at a brisk pace [45] are also risk factors for distal forearm fractures. Among the Japanese population, increased physical activity, in particular increased walking ability, is a risk factor for wrist fractures [46]. This is in agreement with factors identified in previous studies among Caucasians, which concluded that increased physical activity, increased walking ability, and frequent outdoor walking all increase the risk of falls.

On the other hand, a greater frequency of going outdoors significantly decreased the risk of proximal humerus fracture among the Japanese population [46]. This agrees with data from past cohort and case-control studies which identified risk factors for proximal humerus fracture as a low level of physical activity and infrequent walking [47]. The opposite is true for wrist fractures, i.e., wrist fractures are most likely in patients with fragile bones and increased physical activity, while proximal humerus fractures are most likely in patients with fragile bones and decreased physical activity.

One of the significant factors associated with reduced risk of wrist fractures among the Japanese was the use of a futon (as opposed to a bed), which also reduces the risk of hip fracture [24,46]. Futon use might maintain physical activity, resulting in a reduced risk of falls.

Changes in incidence over time

According to our survey performed from 1986 to 1995, the age-adjusted incidence rates of wrist fractures showed a significant increase with time, although no increase was observed among men [1]. Proximal humerus fractures showed a significant increase over time for both sexes. It has been speculated that decreased physical activity associated with a Westernized lifestyle is one possible explanation for the increase in fracture incidence among the Asian population.

Conclusions

In the year 2000, there were an estimated 9.0 million osteoporotic fractures, of which 1.6 million were at the hip, 1.7 million were at the forearm, and 1.4 million were clinical vertebral fractures [48]. It is estimated that the annual number of hip fractures will increase progressively to 2.6 million by the year 2025, and to 4.5 million by 2050 [49]. However, the increase is estimated to be 5 times higher, at 21.3 million, when an annual rate of increase of 3% outside North America and northern Europe is used. This increase will be most marked in Asia.

The percentage of the Japanese population aged 65 years and older will be 23% in 2010, 32% in 2030, and 40% in 2050. Based on the age- and sex-specific incidences observed in the recent study in Tottori, the total number of hip fracture patients in Japan is estimated to be 159000 per year in 2010 and 255000 in 2030. From all these data, we recognize that it is extremely important to implement preventive strategies, which should include the treatment and prevention of osteoporosis, the reduction and prevention of falls, and the maintenance of physical activity among the elderly through lifestyle changes. A reduction in the number of fractures in the elderly is very important in order to reduce the future medical and social burden.

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