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	Mean (Standard Error) $25(OH)D_3$, 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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REFERENCES

1. Riggs BL. Role of the vitamin-D-endocrine system in the pathophysiology of postmenopausal osteoporosis. J Cell Biochem 2003;88:209–215.
2. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477–501.
3. Chapuy MC, Arlot ME, Duboeuf F et al. Vitamin D_3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992;327:1637–1642.
4. Dawson-Hughs B, Harris SS, Krall EA et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670–676.
5. Lips P, Duong T, Oleksik A et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: Baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 2001;86:1212–1221.
6. Nakamura K, Tsugawa N, Saito T et al. Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study. Bone 2008;42:271–277.
7. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351:805–806.
8. Harris SS, Soteriades E, Coolidge JA et al. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. J Clin Endocrinol Metab 2000;85:4125–4130.
9. Sakuma M, Endo N, Oinuma T et al. Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int 2006;17:1608–1614.
10. Stein MS, Wark JD, Scherer SC et al. Falls relate to vitamin D and parathyroid hormone in an Australian nursing home and hostel. J Am Geriatr Soc 1999;47:1195–1201.
11. Drinka PJ. The importance of parathyroid hormone and vitamin D status in the treatment of osteoporosis and renal insufficiency. J Am Med Dir Assoc 2004;5:382–386.
12. Kato C, Ida K, Hoshiyama M et al. Does fall-related self-efficacy in hip-protector users affect quality of life and physical activity in nursing homes in Japan? J Am Geriatr Soc 2010;58:1810–1812.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
14. Nashimoto M, Nakamura K, Matsuyama S et al. Hypovitaminosis D and hyperparathyroidism in physically inactive elderly Japanese living in nursing homes: Relationship with age, sunlight exposure and activities of daily living. Aging Clin Exp Res 2002;14:5–12.
15. Gloth FM, Gundberg CM, Hollis BW et al. Vitamin D deficiency in homebound elderly persons. JAMA 1995;274:1683–1686.
16. McMurtry CT, Young SE, Downs RW et al. Mild vitamin D deficiency and secondary hyperparathyroidism in nursing home patients receiving adequate dietary vitamin D. J Am Geriatr Soc 1992;40:343–347.
17. Delvin EE, Imbach A, Copti M. Vitamin D nutritional status and related biochemical indices in an autonomous elderly population. Am J Clin Nutr 1988;48:373–378.
18. Chapuy MC, Schott AM, Garnero P et al. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter. J Clin Endocrinol Metab 1996;81:1129–1133.
19. Suzuki T, Kwon J, Kim H et al. Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. J Bone Miner Res 2008;23:1309–1317.
20. Gallagher JC, Kinyamu HK, Fowler SE et al. Calciotropic hormones and bone markers in the elderly. J Bone Miner Res 1998;13:475–482.
21. Dawson-Hughe B, Heaney RP, Holick MF et al. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713–716.
22. Bishoff-Ferrari HA, Shao A, Dawson-Hughes B et al. Benefit-risk assessment of supplementation. Osteoporos Int 2010;21:1121–1132.
23. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(4 Suppl 3):S1–S28.
24. Matsuo S, Imai E, Horio M et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–992.
25. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press, 2011.

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ORIGINAL ARTICLE

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

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Abstract

Background Serum 25-hydroxyvitamin D (25(OH)D) is used as an index that reflects the level of vitamin D. We have previously reported, on the basis of a study in Sado in Niigata, that patients with hip fracture have lower serum 25(OH)D levels than non-hip-fracture cases. In this study, the serum 25(OH)D status in hip-fracture cases was examined in four regions in Japan. Although most hip-fracture patients have experienced past spine-compression fractures, the relationship of these fractures and 25(OH)D is unknown. Therefore, we also examined the 25(OH)D level in spine-compression fracture patients in the same locations and time periods.

Methods The levels of 25(OH)D, intact parathyroid hormone (intact PTH), undercarboxylated osteocalcin (ucOC), urine *N*-terminal crosslinking telopeptide of type I collagen (NTX), and bone mineral density were examined in patients with hip and spine fracture due to osteoporosis in several regions in Japan.

Results There were no significant differences in age, BMI, serum 25(OH)D, serum intact PTH, and serum ucOC among the regions. Levels of serum 25(OH)D were low in patients with hip fracture and spine fracture. The average serum 25(OH)D level was significantly lower in hip-fracture patients than in spine-fracture patients (16.3 vs. 18.1 ng/mL, $P < 0.05$). High serum ucOC was found in 37% of hip-fracture patients and 44% of spine-fracture patients.

Conclusions Both hip and spine-fracture patients have vitamin D insufficiency, with similar results found in elderly patients in four areas of Japan. The severity of this condition tends to be more serious in hip-fracture patients than in spine-fracture patients.

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Introduction

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

Table 1 Number of patients in the study

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

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

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

Patients and methods

Study site

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

Subjects

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

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

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

Measurements

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

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

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

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

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

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

Statistical analysis

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

Ethical considerations

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

Results

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

Data in the four regions

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

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

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

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

Comparison of hip and spine fracture

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

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

	Variables/ Regions	Age (years old)	BMI (kg/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

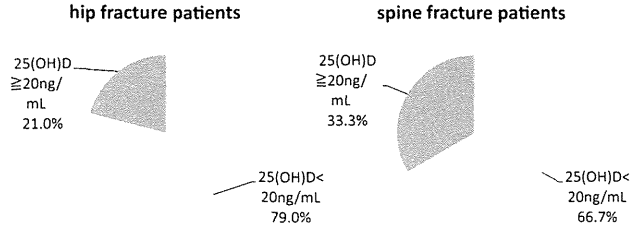

Fig. 1 Percentages of patients with hip or spine fracture with high and low serum 25-OHD levels. The percentages of patients with 25(OH)D < 20 ng/mL were 79.0% in hip-fracture cases and 66.7% in spine-fracture cases

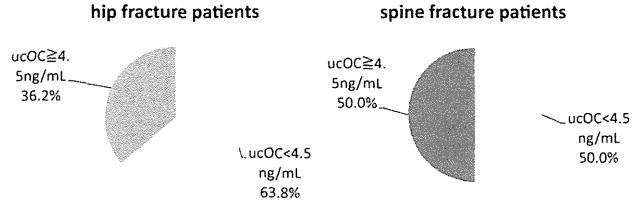

Fig. 2 Percentages of patients with hip or spine fracture with high and low serum ucOC levels. The percentages of patients with ucOC ≥ 4.5 ng/mL were 36.2% in hip-fracture cases and 50.0% in spine-fracture cases

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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References

1. Morita Y, Endo N, Iga T, Tokunaga K, Ohkawa Y. The incidence of cervical and trochanteric fractures of the proximal femur in 1999 in Niigata Prefecture, Japan. J Bone Miner Metab. 2002;20(5):311–8.
2. Oinuma T, Sakuma M, Endo N. Secular change of the incidence of four fracture types associated with senile osteoporosis in Sado, Japan: the results of a 3-year survey. J Bone Miner Metab. 2010;28(1):55–9.
3. Nuti R, Martini G, Valenti R, Gambera D, Gennari L, Salvadori S, Avanzati A. Vitamin D status and bone turnover in women with acute hip fracture. Clin Orthop Relat Res. 2004;422:208–13.
4. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA. 1999;281(16):1505–11.
5. Sakuma M, Endo N, Oinuma T, Hayami T, Endo E, Yazawa T, Watanabe K, Watanabe S. Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int. 2006;17:1608–14.
6. Nakamura K. Vitamin D insufficiency in Japanese populations: from the viewpoint of the prevention of osteoporosis. J Bone Miner Metab 2006;24(1):1–6 (Review).
7. Okano T, Tsugawa N, Suhara Y, Tanaka K, Ishida H, Uenishi K, Kubota E, Fukunaga M, Hosoi T, Shiraki M. Vitamin D status and bone metabolic markers of adult, especially elderly women in Japan. Osteoporos Jpn 2004;12:76–79 (in Japanese).
8. Hagino H, Yamamoto K, Ohshiro H, Nakamura T, Kishimoto H, Nose T. Changing Incidence of hip, distal radius and proximal humerus fractures in Tottori Prefecture, Japan. Bone (NY). 1999;24:265–70.
9. Cummings S, Cauley J, Palermo L, Ross PD, Wasnich RD, Black D, Faulkner K. Racial difference in hip axis length might explain racial differences in rates of hip fracture. Osteoporos Int. 1994;4:226–9.
10. Kanis JA, Johnell O, De Leat C, Jonsson B, Oden A, Ogelsby AK. International variation in hip fracture probabilities : Implication for risk assessment. J Bone Miner Res. 2002;17:1237–44.
11. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317–22.
12. Malabanan A, Veronikis E, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351:805–6.
13. Need AG, Horowitz M, Morris HA, Nordin BC. Vitamin D status: effects on parathyroid hormone and 1,25-dihydroxyvitamin D in postmenopausal women. Am J Clin Nutr. 2000;71:1577–81.
14. Yamaoka M, Inomata K, Wakiya S, Baba H, Yamashita H, Yamashita H, Noguchi S. Zenjidou denkikagaku hakkoumeneki sokuteisouchi "ECLusys 2010" ni yoru fukukoujousenn horumon sokutei no kentou. Jpn J Med Pharm Sci 2001;46(5):753–758 (in Japanese).
15. Thomas L. Parathyroid hormone (PTH). Clinical laboratory diagnosis. 1st English ed. Frankfurt: TH-Books; 1998. pp. 248–250.
16. Segersten U, Correa P, Hewison M, Hellman P, Dralle H, Carling T, Akerstrom G, Westin G. 25-Hydroxyvitamin D(3)-1alpha-hydroxylase expression in normal and pathological parathyroid glands. J Clin Endocrinol Metab. 2002;87(6):2967–72.
17. World Health Organization. Prevention and management of osteoporosis, technical report series 2003; No. 921, pp. 38–31.
18. Tsugawa N, Shiraki M, Suhara Y, Kamao M, Ozaki R, Tanaka K, Okano T. Low plasma phylloquinone concentration is associated with high incidence of vertebral fracture in Japanese women. J Bone Miner Metab. 2008;26(1):79–85.
19. Shiraki M, Aoki C, Yamazaki N, Ito Y, Tsugawa N, Suhara Y, Okano T. Clinical assessment of undercarboxylated osteocalcin measurement in serum using an electrochemiluminescence immunoassay: Establishments of cut-off value to determine vitamin K insufficiency in bone and to predict fracture leading to clinical use of vitamin K2. Jpn J Med Pharm Sci 2007;57(4):537-546 (in Japanese).
20. Nisimura J, Arai N, Tohmatsu J. Measurement of serum undercarboxylated osteocalcin by electro chemiluminescence immunoassay with the "Picolumi ucOC "kit. Jpn J Med Pharm Sci 2007;57(4):523–535 (in Japanese).
21. Kaneki M, Hodges SJ, Hosoi T, Fujiwara S, Lyons A, Crean SJ, Ishida N, Nakagawa M, Takechi M, Sano Y, Mizuno Y, Hoshino S, Miyao M, Inoue S, Horiki K, Shiraki M, Ouchi Y, Orimo H. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. Nutrition. 2001;4:315–21.
22. Tsugawa N, Shiraki M, Suhara Y, Kamao M, Ozaki R, Tanaka K, Okano T. Low plasma phylloquinone concentration is associated with high incidence of vertebral fracture in Japanese women. J Bone Miner Metab. 2008;26:79–85.

COMPLICATION

男性更年期障害と筋肉減少症(サルコペニア)

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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。

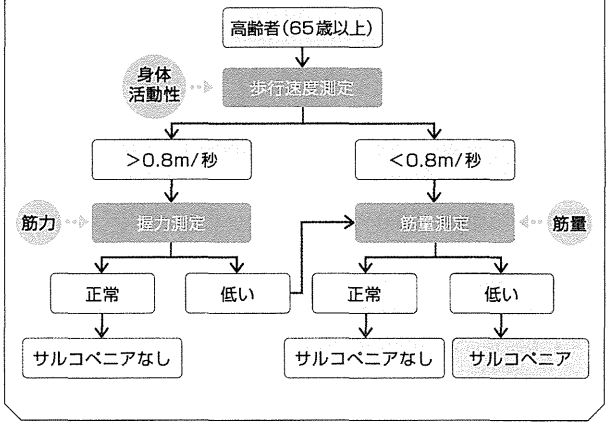
ONE POINT ADVICE

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



文献

1)Wannenes F, et al : Androgen receptor expression during C2C12 skeletal muscle cell line differentiation. Mol Cell Endocrinol 292 : 11-19, 2008
2)Lunenfeld B, et al : ISA, ISSAM and EAU recommendations for the investigation, treatment and monitoring of late-onset hypogonadism in males : scientific background and rationale. Aging Male 8 : 59-74, 2005
3)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:加齢男性性腺機能低下症候群(LOH症候群)診療の手引き.2007 (http://www.urol.or.jp/iryo/guideline/pdf/gl_LOH.pdf)
4)Cruz-Jentoft AJ, et al : Sarcopenia : European consensus on definition and diagnosis : Report of the European Working Group on Sarcopenia in Older People. Age Ageing 39 : 412-423, 2010
5)Roy TA, et al : Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 283 : E284-E294, 2002
6)Krasnoff JB, et al : Free testosterone levels are associated with mobility limitation and physical performance in community-dwelling men : the Framingham Offspring Study. J Clin Endocrinol Metab 95 : 2790-2799, 2010
7)Emmelot-Vonk MH, et al : Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men : a randomized controlled trial. JAMA 299 : 39-52, 2008

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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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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

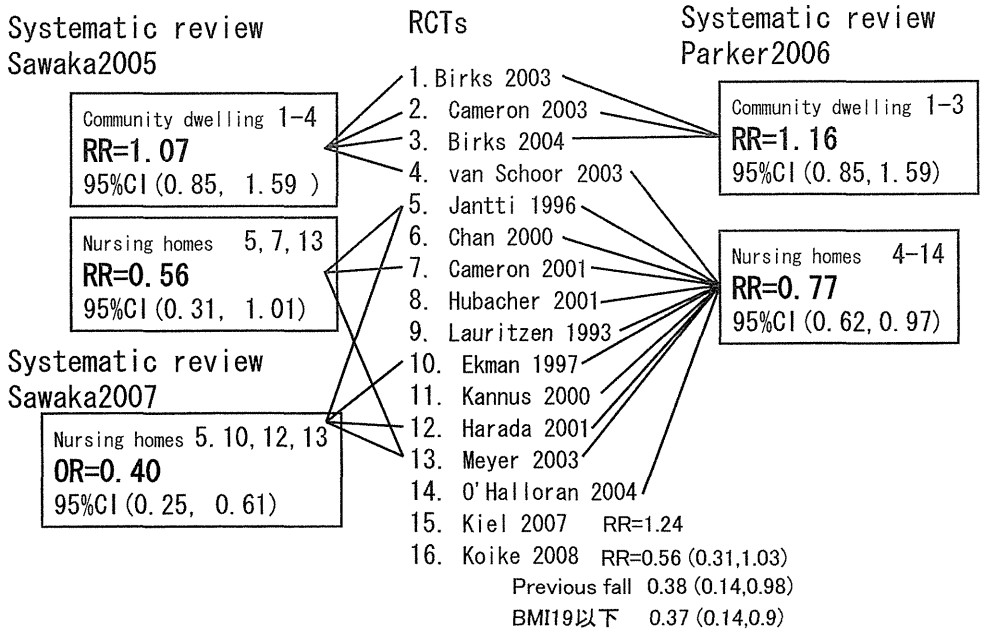

Fig.1　Systematic reviews of randomized controlled trials for hip protectors

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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参考文献

1) Orimo, H., Yaegashi, Y., Onoda, T., Fukushima, Y., Hosoi, T. and Sakata, K.: Hip Fracture Incidence in Japan: Estimates of New Patients in 2007 and 20-year trends, *Arch Osteoporos*, 4 (2009), 71-77.
2) WHO: WHO Global Report on Falls Prevention in Older Age, WHO Library Cataloguing-in-Publication Data, (2007), 1, (http://www.who.int/ageing/publications/Falls_prevention7March.pdf).
3) Matsushita, T., Itoman, M., Nakano, T., Hagino, H., Watanabe, Y., Aoyagi, K., Asayama, A., Kobayasi, A., Sawagudhi, T., Shindo, M., Hayashi, Y., Harada, A. and Yamamoto, N.: *Clinical Guideline forDdiagnosis and Treatment of Hip Fracture* (in Japanese). Ed., x Committee of Clinical Guideline for Diagnosis and Treatment of Hip Fractures in Japanese Orthopaedic Associations, Nankodo, Tokyo, (2005), 37-53.
4) Lotz .JC. and Hayes W.C.: The Use of Quantitative Computed Tomography to Estimate Risk of Fracture of the Hip from Falls, *J Bone Joint Surg*, 72-A (1990) 689-700.
5) Courtney A.C., Wachtel E.F., Myers E.R. and Hayes W.C.: Age-related Reductions in the Strength of the Femur Tested in a Fall-loading Configuration, *J Bone Joint Surg*, 77-A (1995), 387-395.
6) Cheng X.G., Lowest G., Boonen S., Nicholson P.H., Van der Perre G. and Dequeker J.: Prediction of Vertebral and Femoral Strength in Vitro by Bone Mineral Density Measured at Different Skeletal Sites, *J Bone Miner Res*, 13 (1998), 1439-1443.
7) Okuizumi, H., Harada, A., Iwata, H. and Konishi, N.: Effect on the Femur of a New Hip Fracture Preventive System using Dropped-weight Impact Testing, *J Bone Miner Res*, 13 (1998), 1940-1945.
8) Wakao, N., Harada, A., Matsui, Y., Takemura, M., Shimokata, H., Mizuno, M., Ito, M., Matsuyama, Y. and Ishiguroa, N.: The Effect of Impact Direction on the Fracture Load of Osteoporotic Proximal Femurs, *Medical Engineering & Physics*, 31-9 (2009), 1134-1139.
9) Robinovitch S.N., Hayes W.C. and McMahon T.A.: Prediction of Femoral Impact Forces in Falls on the Hip, *J Biomech Eng.*, 113 (1991), 366-374.
10) Gillespie L.D., Robertson M.C., Gillespie W.J., Lamb S.E., Gates S., Cumming R.G. and Rowe B.H.: Interventions for Preventing Falls in Older People Living in the Community, *Cochrane Database of Systematic Reviews* (2009) Issue 2. Art. No.: CD007146. DOI:10.1002/14651858.CD007146.pub2.
11) Parker M.J., Gillespie W.J. and Gillespie L.D.: Effectiveness of Hip Protectors for Preventing Hip Fractures in Elderly People: Systematic Review, *BMJ*, 332 (2006), 571-574.
12) Harada, A., Matsui, Y., Mizuno, M., Tokuda, H., Nino, N. and Ohta, T.: Hip Fracture Prevention Trial using Hip Protectors in Japanese Nursing Homes, *Osteoporos Int.*, 12 (2001), 215-221.
13) Robinovitch S. N., Evans S. L., Minns J., Laing A. C., Kannus P., Cripton P. A., Derler S., Birge S. J.: Plan D., tCameron I. D., Kiel D. P., Howland J., Khan K. and Lauritzen J. B.: Hip Protectors: Recommendations for Biomechanical Testing - an International Consensus Statement (part I), *Osteoporos Int.*, 20 (2009) , 1977-1988.

骨粗鬆症における発症と骨折予防●骨粗鬆症の骨折予防

骨外因子

原田　敦

骨折は，骨折指数が1を超えると起こる。骨折指数とは，骨のもつ圧縮・引っ張り強さで骨に加わる圧縮・引っ張り主応力を除した式で表され，簡単にいえば外力と骨強度の比で，骨強度が骨内因子，外力が骨外因子である（**図1**）。

骨強度に関しては，これまで多くの基礎，疫学，臨床の研究データの蓄積がなされており，その上に有効な薬剤が多く使用可能になってきていて，骨強度の改善を介する骨折予防は，大きな発展を遂げている。一方，外力に関しては，その発生から骨折に至るまでの過程に対して，同様な範疇の十分な科学的データが蓄積されたとはまだいえない状況である。たとえば，転倒が起こってから大腿骨近位部骨折が生じるまでのメカニズムを詳細に明瞭に示すデータはまだ乏しく，特に高齢者に限ると極めて限られている。その背景には，高齢者の転倒には多様な様式があり，そこから受ける外力の条件もごく軽度のレベルから重度のものまで幅広く，それぞれについて実際の転倒が起こる現場のデータが必要であるにもかかわらず，その入手は困難であり，結局，転倒の有無や回数にデータ収集が留まりがちであるからである。さらに，実際の転倒や，転倒で骨折を起こす過程を実証試験で確かめることは安全面から実施不可能という状況もある。

とはいえ，撓骨遠位端，上腕骨近位部，脊椎など，各好発部位のうち，大腿骨近位部骨折に関しては上記に関する知見もある程度そろっているので，この稿では，骨外因子による大腿骨近位部骨折を中心に骨外因子による骨粗鬆症性骨折予防を取りあげる。

前述したように，骨外因子とは外力であり，その主要な力源は転倒である。したがって，転倒外力に対抗する方法に基づく骨折予防は，転倒外力の発生機会を減らす方法と，生じた転倒外力による外傷を軽減化する方法の二つにわかれる。

転倒外力の発生機会を減らす方法は，転倒予防と言い換えることができる。転倒の内的要因のう

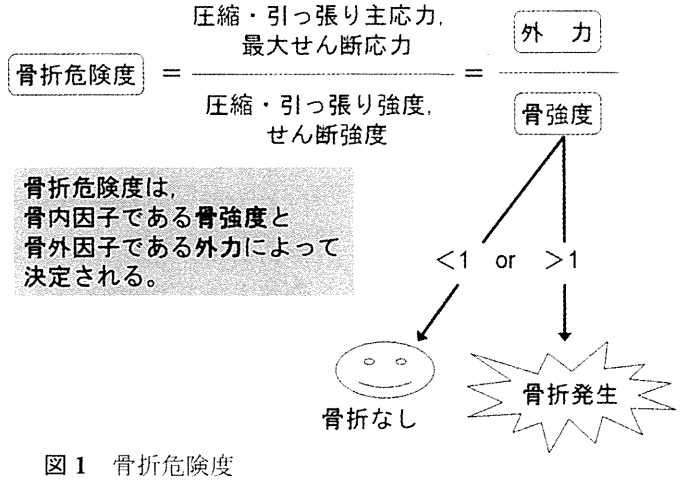

図1　骨折危険度

Key words：骨強度，転倒外力，運動器不安定症，ヒッププロテクター

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表1　運動器不安定症の定義と診断

定義：高齢化により，バランス能力および移動歩行能力の低下が生じ，閉じこもり，転倒リスクが高まった状態

診断：下記の運動機能低下をきたす疾患の既往・罹患がある者で，日常生活自立度あるいは運動機能が以下に示す機能評価基準1または2に該当する者

運動機能低下をきたす疾患

- 脊椎圧迫骨折および各種脊椎変形
- 下肢骨折
- 骨粗鬆症
- 変形性関節症
- 腰椎脊柱管狭窄症
- 脊髄障害
- 神経・筋疾患
- 関節リウマチおよび各種関節炎
- 下肢切断
- 長期臥床後の運動器廃用
- 高頻度転倒者

機能評価基準

1. 日常生活自立度：ランクJまたはA
（要支援＋要介護1，2）

あるいは

2. 運動機能1）または2）
1）開眼片足起立時間15秒未満
2）3m Timed up and go test 11秒以上

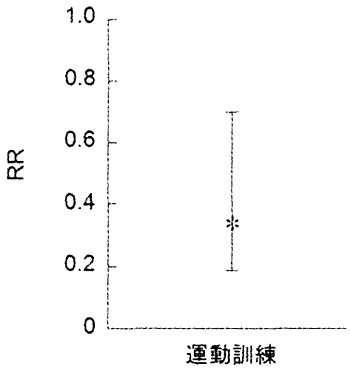

図2　転倒予防介入試験（RCT）による骨折予防成績[3]

ち最たるものである筋力バランスの低下による易転倒性である。これは運動器不安定症という概念でまとめられ（**表1**），保険病名として扱うことができるようになっていることは，世界に誇るべきわが国の成果であると考える。この診断基準にあてはまる高齢者に，開眼片足立ちや膝伸展訓練などの運動療法で転倒が減少することが報告されている[1,2]。このように，運動器不安定症の診断に基づき，下肢の筋力バランス低下に対する運動介入が，クリニックを中心に幅広く外来治療として実践できる体制が築かれたことは，転倒予防の大きな基盤である。このような筋力強化とバランス改善のプログラムや太極拳は，複数のメタアナリシスで転倒抑制の有効性が高いレベルのエビデンスをもって示されている。家庭環境因子の評価と改善，向精神薬中止，心臓ペースメーカー，多角的プログラムなども転倒を減らす高いレベルのエビデンスがあり，転倒リスク低減を目標とする場合には，転倒リスクに応じた介入を行えば，高い有用性が期待できるといえる。ただ，これらが転倒による重度の外傷予防に有効であるかについては，運動訓練5試験（719名）のメタアナリシスにおいて，脊椎骨折を除いて解析したところ，大腿骨近位部以外の四肢骨折が減少し，この結果はパーキンソン病患者の試験を除外しても有意であったと報告されている（**図2**）[3]。このように，まだ限られてはいるが，運動訓練による骨折予防のエビデンスが示されるようになった。

生じた転倒外力による外傷を軽減化する方法としては，転倒時のつかまりや体の回転など，本能的な防御動作は大きな役割を果たすと考えられるが，この過程に関する解明は高齢者においては不十分で，今後の大きな課題である。高いレベルのエビデンスを備えるのは，目標が大腿骨近位部骨折に限られるが，大転子部の衝撃を緩和する

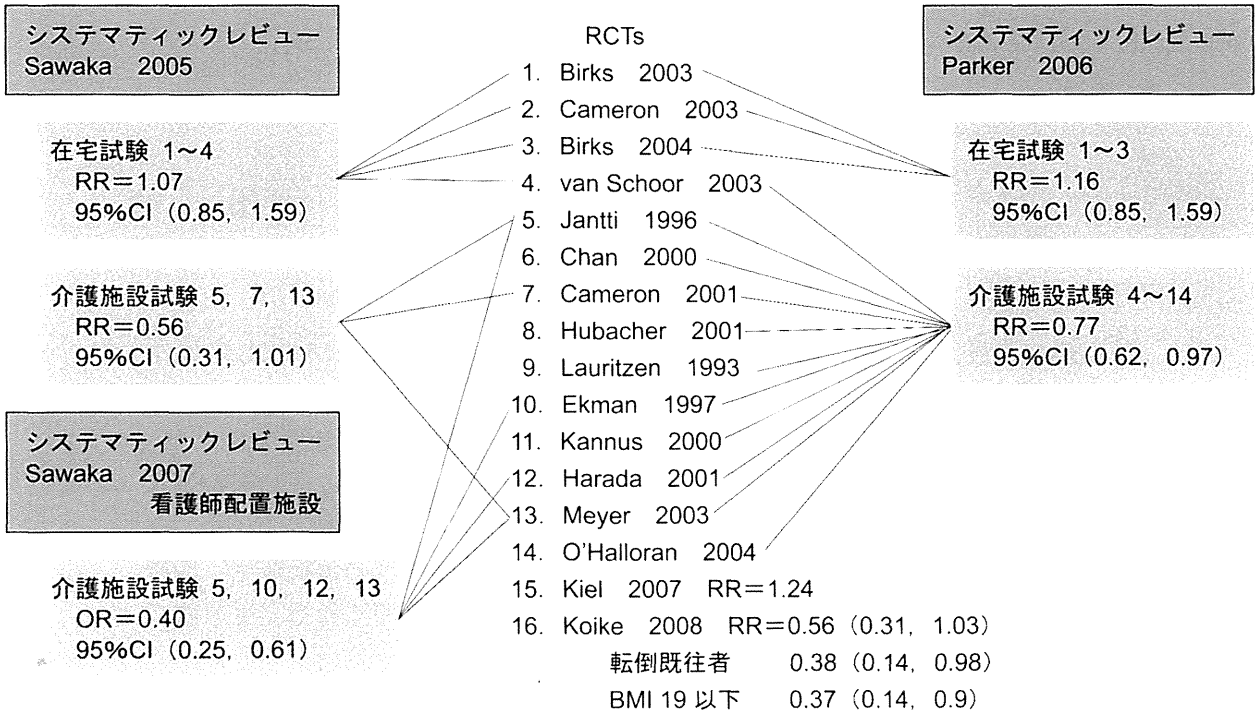

図3　ヒッププロテクターのRCTとシステマティックレビュー[4]

ヒッププロテクターで，多数のRCTをまとめたいくつかのシステマティックレビューによれば，大腿骨近位部骨折は，介護施設では明らかに有意な減少を示し，看護師配置の介護施設に限ると有効性はより高くなるとされている。介護施設や病院に入院している高齢者で，いつ転んでもおかしくないような高い転倒リスク者に適応すれば高い有効性が期待できる。一方，転倒リスクの低い在宅高齢者での有効性は認められていない（図3）[4]。製品の品質向上は続いており，今後のさらなる発展が期待される。

文　献

1) Sakamoto K, Nakamura T, Hagino H, et al; Committee on Osteoporosis of The Japanese Orthopaedic Association. Effects of unipedal standing balance exercise on the prevention of falls and hip fracture among clinically defined high-risk elderly individuals: a randomized controlled trial. J Orthop Sci 2006;11:467-72.
2) Kita K, et al. A simple protocol for preventing falls and fractures in elderly individuals with musculoskeletal disease. Osteoporos Int 2007;18:611-9.
3) Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community (Review). Cochrane Database of Systematic Reviews. 2009; Issue 2.Art.No.: CD007146.DOI:10.1002/14651858.CD007146.pub2.
4) 原田　敦．ヒッププロテクターの骨折予防効果．日本医師会雑誌 2009;137:2286.

Geriat. Med. 49(9)：961～962, 2011

序文

原田　敦

骨粗鬆症の最大の合併症である骨折は，高齢者の機能予後およびQOLを悪化させ，さらに生命予後も低下させていることが最近判明している[1]．そこに示される大腿骨近位部骨折に限らず，高齢者がいったん骨粗鬆症性骨折を起こすと，その後の骨折リスクはさらに大きく上昇し，骨折治療後も少なくとも一部の患者は“虚弱”に陥り，先死期に入っていく状況が示唆されるものである．しかしながら，近年の骨粗鬆症の診療の大いなる進歩によって，高齢者の骨折発生，機能低下，QOL低下，生命予後悪化の悪循環を止めて，その扉を開く骨折発生を防ぐことが可能になりつつある．

骨粗鬆症診療は，この20年間ほどにわたり，飛躍的進歩を遂げてきた．その発展に最も寄与した礎は，定義の進歩である．「低骨密度と構造の異常により骨折危険性が増した状態」という定義を1994年にWHOが決定し，骨粗鬆症診療の最終目標が，骨密度や骨代謝の改善ではなく，骨折危険性の低下にあることが共通認識となった．さらに，「骨強度の低下を特徴とし，骨折危険性が増大しやすくなる骨格疾患」と2000年にNIHコンセンサス会議が修正し，骨強度という極めて妥当な概念を定着させ，骨粗鬆症診療は骨強度の維持・改善を通じて骨折危険性の低下を図る医療であることが明確化された．したがって，骨粗鬆症の診断＝骨強度の評価による骨折リスクの予測，骨粗鬆症の治療＝骨強度への有効な介入による骨折リスクの低減という図式が成り立って，現在に至っている．

さらに，NIHコンセンサスで記述された骨強度は，70%が骨密度，30%が骨質（微細構造，骨代謝回転，微小骨折，石灰化など）によって規定されるという説明が普及した．つまり，骨折リスクを正しく把握するためには，骨密度だけでは不十分であるという認識で，骨粗鬆症の診断手段上，それを補う手段として日常診療で実施可能なものは，骨吸収および骨形成に関する各種骨代謝マーカーによって骨代謝回転の動向を推定したり，日本人長期縦断疫学データから得られた大腿骨近位部骨折などの骨粗鬆症性骨折の頻度を根拠として，既往歴などの臨床危険因子を使用して，たとえ骨密度データがなくても10年間の骨折確率推定値を得られるFRAXである．さらに，骨の3次元構造や骨密度分布を骨強度計算に反映させた測定（CT有限要素法は先進医療に認定）が，2次元骨密度を超える方法として登場している．さらに，大きな注目を浴びているのが，骨コラーゲンへの終末糖化・酸化産物の過形成をペントシジンやホモシステインで評価して骨質異常を判定して，骨密度診断と合わせて骨折リスクをより精度を高く予測しようとする方法で，その研究がわが国で大きく進展した．

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一方，骨粗鬆症診療は治療面でも大きな前進が重ねられ，元々，わが国独自の発展がみられた活性型ビタミンD製剤やビタミンK_2製剤に加えて，強力な骨折予防エビデンスを備えた第2世代以降のビスフォスフォネート製剤と，選択的エストロゲン受容体モジュレーター(SERM)が日常診療で使える薬剤として普及定着し，その後，しばらく新薬は登場しなかったが，この3年ほどで，わが国で開発されたビスフォスフォネート製剤と新型活性型ビタミンD製剤が新しく臨床で使用できる薬剤として加わり，さらに新型SERMとこれまでの骨吸収抑制が主体の薬剤体系に骨形成促進が期待できるPHTが登場したことで，患者の有する多様な骨折リスク条件を考慮しながら，新しい薬剤治療を組み立てることが以前と比べて容易になってきた．さらに，まだ市販には至らないものの，いっそう強力な有効性が期待できる抗RANKL抗体なども控えている．

本特集では，骨粗鬆症の診断と治療の最近の発展について，総論と各論に分けて，読者にそれぞれの最新の情報をわかりやすくお届けすることができるようにするとともに，老年医学分野で非常に重要な位置を占める虚弱という病態に骨粗鬆症がどう関連するかについて，そして，薬剤以外の骨粗鬆症診療として欠かせない運動療法や大腿骨近位部骨折の予防エビデンスのあるプロテクターについての解説を，各分野における第一人者にお願いした．本特集が老年医療に関わっておられる皆様に少しでもお役に立てば幸いである．

文　献

1) Tsuboi M et al：Mortality and mobility after hip fracture in Japan：a ten-year follow-up. J Bone Joint Surg Br **89**：461-466，2007.

1．サルコペニアの定義，診断基準

原田　敦*
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- 加齢に伴なう筋量と筋力の低下は，サルコペニアと呼ばれ，補正四肢筋量による診断がスタンダードとされていた．
- サルコペニアは，The European Working Group on Sarcopenia in Older People によって，「筋量と筋力の進行性かつ全身性の減少に特徴づけられる症候群で，身体機能障害，QOL 低下，死のリスクを伴うもの」とされた．
- そこでは，筋量だけでなく，筋力，身体機能から診断するアルゴリズムが提示された．
- 別グループからは，筋量と移動能力が基準値より低下したサルコペニアに，介入するという提案もなされている．
- 定義，診断基準ともにまだ流動的である．

Key Words　サルコペニア，筋量，筋力，身体機能

□ サルコペニアの定義，診断基準に関する歴史的経緯

サルコペニアの定義にはまだ確定したものはない．診断基準も流動的であることを最初にお断りする．本稿ではこの2年ほどの間で新しく国際的に提案されたものを中心に記載する．

最初に骨粗鬆症の定義の経緯に触れる．骨粗鬆症は定義が病理学的概念に留まっていた時期が長くあり，疾患として高い注目を浴びる存在ではなく，社会のニーズも高くはなかった．しかし，高齢社会の到来とともに重要性は増し，骨粗鬆症は骨折の危険が高まった状態とされ，WHO（世界保健機関）は，「全身疾患であり，骨量の減少と構造の異常により骨の強度が減少し，骨折の危険性が高まった状態」とした[1]．そこから診断治療の目標は明瞭に骨折の危険性の減少とされ，カットオフ値も若年成人平均値（young adult mean：YAM）から2標準偏差（standard deviation：SD）を引いた値と明記され，この値は骨折リスク上昇とよく一致し，その後の大きな骨粗鬆症医学の発展のゆるぎない土台となった．

次に筋肉に関しても，加齢とともに減少することは古くから知られ，老化によるもので自然な現象と受け入れられ，初期の骨粗鬆症に似た捉え方がされていたが，加齢に伴う筋力と筋量の低下という疾患概念にサルコペニア（sarcopenia）という名称を与えたのはRosenbergで1989年のことである．その由来は，sarco（ギリシャ語の肉）とpenia（ギリシャ語の減少）の組み合わせである[2]．ただ，定義の根幹となる疾患の一義的アウトカムが何であるかについての明瞭な記載はなく，曖昧であった．

一方，その頃，急速に普及しつつあった骨粗鬆症診断で有力な二重エネルギーX線吸収法（dual energy x-ray absorptiometry：DXA）は，骨量測定だけでなく，筋量測定にも大きな進歩をもたらした．全身および各部位における脂肪量の高精度の算定によって，骨量と軟部組織量の計測能が大きく向上し，DXA全身モードによって容易に正確で再現性のよい筋量測定ができるようになった[3]．その測定は簡便で，検者間誤差が少なく，信頼性が高い測定値が得られる．筋量に対する変動係数は0.6～1.6%とされている[4]．

全身各部位のうち，四肢筋量なら神経や血管等の筋以外の組織が含まれるものの，その量はわずかであり，実際の筋量にもっとも近似すると考えられる．そこで，両側の上肢と下肢の和を四肢筋量とする概念が提示された[5]．さらにBaumgart-

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ner が DXA による四肢筋量が，誤差 3.0% で CT や MRI で測定した場合と 5% 以下の高い信頼性を有することを確認したうえで，強く相関する身長・性差・人種差の影響を効率的に除外できる調整法として，下記の式によって求められる補正四肢筋量を提唱した．同時に，白人一般住民男女の補正四肢筋量の若年成人（18～40 歳）平均値（YAM）から 2SD を引いた値である男性 7.26 kg/m^2，女性 5.45 kg/m^{2}をサルコペニアと診断する際のカットオフ値として提案した[6]．

補正四肢筋量＝四肢筋量（kg)/身長（m)^2

この補正四肢筋量の考え方は画期的で，当時の学会に大きな影響を与え，この手法でサルコペニアの有病率などを検討する研究が続いた．ただ，サルコペニアの定義や治療目標について新たな言及はされないまま，診断に際して補正四肢筋量による筋量が重要視される傾向が次第に形成された．しかし，何よりも一義的アウトカムが明確でないまま設定されたので，診断で使用するカットオフ値である YAM－2SD の正当性の検証が困難だったことも大きい．しかも，白人のカットオフ値は決められたが，他の人種についてはデータが乏しいままに経過し，その間白人以外の診断はあきらめざるを得なかった．

一方，筋量と筋力の扱いでは筋量が優先される傾向が続いているが，筋量を増強させる介入は必ずしも筋力を増やすとは限らない[7]．さらに，高齢者においては，筋量変化と筋力変化の相関は一定でなく，それほど強いものではないこと[8]など，筋量と筋力の関係が必ずしも一定でないことも示されるようになった．その一定性を欠く理由の 1 つとして，筋内脂肪浸潤で sarcopenic obesity と命名されたこと[9]など，筋量に対する信頼性が揺らぐデータも多く出されている．

□ The European Working Group on Sarcopenia in Older People（EWGSOP）のコンセンサスによるサルコペニアの定義

このように，この 10 年ほどは十分な定義がないままに推移したが，2010 年に EWGSOP によるコンセンサスが発表され，サルコペニアの定義や診断基準に関して，現時点で可能な範囲の整理統合を行うとともに新しい分類の提唱がなされ，サルコペニアの診療と研究に新しい流れをもたらすきっかけとなった[10]．

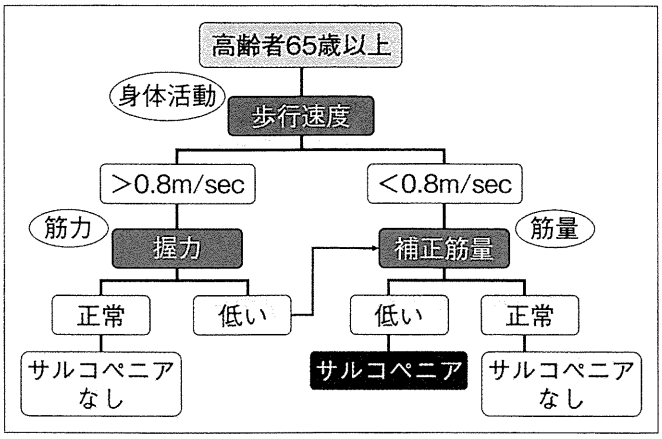

図 1　EWGSOP のコンセンサスによる「サルコペニア」の診断手順
(Cruz-Jentoft AJ, et al.：Age and Ageing 39：412-423, 2010 より引用して改変)[10]

EWGSOP コンセンサスでは，サルコペニアとは「筋量と筋力の進行性かつ全身性の減少に特徴づけられる症候群で，身体機能障害，QOL 低下，死のリスクを伴うもの」とされた[10]．つまり，ここで初めて，幅広い有識者の合意として，サルコペニアが，身体機能障害，QOL 低下，そして死の 3 つのリスクに影響するものと記載された．見方を変えれば，1 つのリスクに絞れなかったとも読める結果であった．いずれにしてもサルコペニアは，進行すれば，高齢者に虚弱（frailty）や移動能力低下などをもたらし，身体的自立喪失，すなわち，要介護化の危険性を上昇させる．また，定義には加齢や年齢という用語は使われていない．

□ EWGSOP のコンセンサスによるサルコペニアの診断基準

EWGSOP コンセンサスでは，筋量の減少と筋力の減少が身体活動障害をもたらす症候群と定義されたので，診断基準も筋量，筋力，身体活動の三要素から構成された．つまり，筋量の減少は必須条件とされ，それに筋力の減少か，または身体活動低下のどちらかが加われば，サルコペニアと診断される[10]．

また，病期分類も新しく設定され，筋量減少の