

Table 4 The accomplished ratio (%) of IADL items compared between subjects with and without trunk deformity. Kruskal-Wallis test: among five groups, Mann-Whitney test: between with (II-V) and without trunk deformities (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

Classification	I	II	III	IV	V	P-value	II-V	P-value
Going out using public transportation	93.1(%)	82.2(%)	75(%)	76.9(%)	77.8(%)	0.04	78.4(%)	0.003
Shopping for groceries	100	95.6	94.6	96	100	0.24	95.8	0.037
Preparing meals	98.1	93.5	91.9	92.3	100	0.37	93.3	0.09
Paying bills	99	93.3	94.6	92.3	100	0.27	94.1	0.052
Depositing and withdrawing money	98	91.3	91.9	88.5	100	0.17	91.7	0.035
Writing paper	93.2	83	86.5	80	100	0.13	85	0.053
Reading newspaper	82.4	75.6	67.6	76.9	90.9	0.32	74.8	0.17
Reading magazine or book	81	72.1	72.2	72	81.8	0.66	73	0.17
Taking an interest in news of health	97	90.7	86.5	91.7	100	0.17	90.4	0.052
Visiting friends	79	78.6	73	80	81.8	0.94	77.4	0.78
Giving advice to family or friend	85.1	75	73	80	100	0.19	77.6	0.16
Visiting friend in the hospital	98	89.1	91.9	88.5	100	0.12	90.8	0.023
Talking to young people	92.2	87	86.5	80.8	90.9	0.52	85.8	0.14

Table 5 Geriatric depression scale (GDS) by the classification of trunk deformity. *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean	SD	95% confidence intervals
I	5.8	3.65	-1.5; 13.1
II	5.9	3.79	-1.68; 13.48
III	6.6	3.76	-0.92; 14.12
IV	6.4	3.14	0.12; 12.68
V	5.4	3.78	-2.16; 12.96
II-V	6.2	3.62	-1.04; 13.44

abnormal trunk deformity group was more limited than that of normal participants. In contrast, kyphosis is associated with decreased bone mineral density (BMD) and loss of height, but does not cause substantial chronic back pain, disability, or poor health in older women [7]. However, previous studies have not assessed patterns of trunk deformity in the context of detailed assessments of functional impairment of daily living in the elderly.

In this study, we classified trunk deformity into five groups: I normal; II thoracic kyphosis; III lumbar kyphosis; IV flat back; and V lumbar lordosis. Previously, we reported that standing trunk posture was closely associated not only with distance and time parameters of gait, but also with functional performance measures

such as functional reach and timed up and go tests in elderly subjects dwelling in a rural community [17]. In the present study, we evaluated if trunk deformity is associated with the results of a detailed assessment of indoor and outdoor activities of daily living, satisfaction with life, and mental status.

This study demonstrated that the lumbar kyphosis group had decreased activities of daily living, manifested primarily in the basic ADL of walking. Of the IADL, the trunk deformity group exhibited decreased activities of daily life such as going out, shopping, depositing and withdrawing money, and visiting friends in the hospital. These activities require going out of doors. This means the abnormal trunk deformity group experienced limited outdoor activities. The lumbar kyphosis group had greater interest in their own health, possibly because they have plenty of time to think about their own health at home, as their outdoor activities are limited.

So far, few reports have discussed the association between trunk deformity and mental status. However, vertebral deformity was shown to be associated with psychological morbidity in elderly Chinese women [28].

With regard to subjective healthiness and life satisfaction, there was no significant difference among the trunk deformity groups; however, the abnormal posture group tended to score lower than the normal group on measures of their own subjective health condition, everyday feeling, satisfaction with human relationships,

Table 6 Satisfaction-with-life score by the trunk deformity. Mann-Whitney test: between with (II-V) and without trunk deformities (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean; SD		P-value
	Normal (I)	Abnormal (II-V)	
Subjective health condition	64.9; 17.85	59.3; 18.75	0.033
Everyday feeling	68.5; 18.56	61.7; 19.52	0.007
Satisfaction with human relationship to others	80.8; 16.31	77.6; 19.17	0.29
Satisfaction with human relationship to family	82.1; 14.55	77.5; 16.61	0.035
Satisfaction with economic condition	62.1; 20.91	55.6; 22.72	0.03
Satisfaction with present life	68.3; 20.55	62.5; 23.2	0.051
Subjective happiness	67.1; 20.09	64.0; 21.37	0.32
Total	457.8; 181.07	428.7; 155.95	0.08

satisfaction with economic condition, and satisfaction with present life. Therefore, the trunk deformity group experienced less subjective healthiness and satisfaction with life. This result may be explained by the limitation of outdoor activities that can lead to a limited social life and difficulty in enjoying a healthy and active life in the community.

Schreiner et al. reported that Geriatric Depression Scale was accurate and reliable in dementia among Japanese subjects [29]. Although the subjective impression of mental status in the trunk deformity group was not as favorable as that of normal group, the GDS in the trunk deformity group did not reveal significant difference in that of normal group. In another study, a significant association was found between BMD of the hip and depressive symptoms after adjustment for osteoporosis risk factors [30]. They suggested the relationship between low BMD and depression was associated with endogenous steroid. We should evaluate the GDS of the larger number of participants by the classification of trunk posture and detailed background of participants to clarify the relation of depression and spinal deformity.

In this study, we did not take X-rays of thoracic and lumbar lesions in the participants, and therefore cannot speculate on the association between spinal posture and vertebral fracture. Further examinations of the radiography of spine and bone densities, such as dual energy X-ray absorptiometry (DXA) or quantitative ultrasound, are necessary to assess the association between spinal posture and vertebral osteoporosis in the community-dwelling elderly. Further studies are also needed to evaluate the cause of the limitation in outdoor activities experienced by study participants with lumbar kyphosis, and to clarify and assess the relationship between mental status and trunk deformity through long-term follow-up.

In conclusion, patients in this study with trunk deformities exhibited decreases in activities that require going outdoors. The abnormal trunk deformity groups also tended to score lower than the normal group with regard to subjective healthiness and life satisfaction measures.

References

1. Takemitsu Y, Harada Y, Iwahara T, Miyamoto M, Miyatake Y (1988) Lumbar degenerative kyphosis: clinical, radiological and epidemiological studies. *Spine* 13:1317-1326
2. Lee CS, Lee CK, Kim YT, Hong YM, Yoo JH (2001) Dynamic sagittal imbalance of the spine in degenerative flat back. Significance of pelvic tilt in surgical treatment. *Spine* 26:2029-2035
3. Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly persons living in the community. *N Engl J Med* 319:1701-1706
4. Maki B, Holliday P, Topper A (1994) A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. *J Gerontol* 49: M72-84
5. Gelb DE, Lenke LG, Bridwell KH, Blanke K, McEneaney KW (1995) An analysis of sagittal spinal alignment in 100 asymptomatic middle and older aged volunteers. *Spine* 20:1351-1358
6. Krebs DE, Wong D, Jevsevar D, Riley PO, Hodge WA (1992) Trunk kinematics during locomotor activities. *Phys Ther* 72:505-514
7. Ettinger B, Black DM, Palermo L, Nevitt MC, Melnikoff S, Cummings SR (1994) Kyphosis in older women and its relation to back pain, disability and osteopenia: the study of osteoporotic fractures. *Osteoporos Int* 4:55-60
8. Cook DJ, Guyatt GH, Adachi JD, Clifton J, Griffith LE, Epstein RS, Juniper EF (1993) Quality of life issues in women with vertebral fractures due to osteoporosis. *Arthr Rheum* 36:750-756
9. Ensrud KE, Black DM, Harris F, Ettinger B, Cummings SR (1997) Correlates of kyphosis in older women. The Fracture Intervention Trial Research Group. *J Am Geriatr Soc* 45:682-687
10. Ryan PJ, Blake G, Herd R, Fogelman I (1994) A clinical profile of back pain and disability in patients with spinal osteoporosis. *Bone* 15:27-30
11. Hall SE, Criddle RA, Comito TL, Prince RL (1999) A case-control study of quality of life and functional impairment in women with long-standing vertebral osteoporotic fracture. *Osteoporos Int* 9:508-515
12. Lyles KW, Gold DT, Shipp KM, Pieper CF, Martinez S, Mulhausen PL (1993) Association of osteoporotic vertebral compression fractures with impaired functional status. *Am J Med* 94: 595-601
13. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J (2000) Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res* 15:1384-1392
14. Miyakoshi N, Abe E, Shimada Y, Okuyama K, Suzuki T, Sato K (2000) Outcome of one-level posterior lumbar interbody fusion for spondylolisthesis and postoperative intervertebral disc degeneration adjacent to the fusion. *Spine* 25:1837-1842
15. Takahashi T, Wada Y, Tanaka M, Iwakawa M, Ikeuchi M, Hirose D, Yamamoto H (2000) Dome-shaped proximal tibial osteotomy using percutaneous drilling for osteoarthritis of the knee. *Arch Orthop Trauma Surg* 120:32-37
16. Ando M, Yamamoto H, Nakatani K, Otani M (1986) Low back pain and trunk posture of elder people in a rural district. *Seikeigeka bessatu* 12:14-17 (in Japanese)
17. Hirose D, Ishida K, Nagano Y, Takahashi T, Yamamoto H (2004) Posture of the trunk in the sagittal plane is associated with gait in community-dwelling elderly population. *Clin Biomech* 19:57-63
18. Staffel F (1989) Die menschlichen haltungs typen. J.F. Bergmann, Wiesbaden
19. Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y (1999) Frailty in elderly Japanese. *Lancet* 353:1445
20. Gerety C (1982) Medical evaluation of the geriatric patient. In: Katz MS (ed) *Geriatric medicine*. Churchill Livingstone, New York
21. Norris JT, Gallagher D, Wilson A, Winograd CH (1987) Assessment of depression in geriatric medical outpatients: the validity of two screening measures. *J Am Geriatr Soc* 35:989-995
22. Morrison DP (1983) The Crichton Visual Analogue Scale for the assessment of behaviour in the elderly. *Acta Psychiatr Scand* 68:408-413
23. Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y (1997) Quality of life of old people living in the community. *Lancet* 350:1521-1522
24. Liu-Ambrose T, Eng JJ, Khan KM, Mallinson A, Carter ND, McKay HA (2002) The influence of back pain on balance and functional mobility in 65- to 75-year-old women with osteoporosis. *Osteoporos Int* 13: 868-873
25. Huang C, Ross PD, Wasnich RD (1996) Vertebral fracture and other predictors of physical impairment and health care utilization. *Arch Int Med* 156: 2469-2475
26. Jinbayashi H, Aoyagi K, Ross PD, Ito M, Shindo H, Takemoto T (2002) Prevalence of vertebral deformity and its associ-

- ations with physical impairment among Japanese women: the Hizen-Oshima Study. *Osteoporos Int* 13:723-730
27. Ryan SD, Fried LP (1997) The impact of kyphosis on daily functioning. *J Am Geriatr Soc* 45:1479-1486
 28. Lau EMC, Woo J, Chan H, Chan MKF, Griffith J, Chan YH, Leung PC (1998) The health consequences of vertebral deformity in elderly Chinese men and women. *Calcif Tissue Int* 63:1-4
 29. Schreiner AS, Hayakawa H, Morimoto T, Kakuma T (2003) Screening for late life depression: cut-off scores for the Geriatric Depression Scale and the Cornell Scale for depression in dementia among Japanese subjects. *Int J Geriatr Psychiatr* 18:498-505
 30. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T (2001) The association of bone mineral density and depression in an older population. *J Am Geriatr Soc* 49:732-736

VERTICAL GROUND REACTION FORCE SHAPE IS ASSOCIATED WITH GAIT PARAMETERS, TIMED UP AND GO, AND FUNCTIONAL REACH IN ELDERLY FEMALES

Toshiaki Takahashi,¹ Kenji Ishida,¹ Daisuke Hirose,¹ Yasunori Nagano,¹ Kiyoto Okumiya,² Masanori Nishinaga,² Yoshinori Doi² and Hiroshi Yamamoto¹

From the ¹Department of Orthopaedic Surgery, Kochi Medical School, Kochi, ²Department of Medicine and Geriatrics, Kochi Medical School, Kochi, Japan

Objective: The aim of this study was to evaluate the relationship between knee pain and various indicators of the combined performance of the lower extremity (including gait parameters, functional performance such as timed up and go, and functional reach test) and to determine whether the classification of vertical ground reaction forces correlates with gait parameters and functional performance.

Subjects and Methods: Simultaneous analysis of gait, time-distance parameters and vertical ground reaction force. Timed up and go, and functional reach test were examined in 130 elderly women. The vertical component of the ground reaction force was grouped into 2 categories: M-shaped and non-M-shaped.

Results: No significant association was found between knee pain and timed up and go, functional reach test, or gait parameters in elderly female participants. There were significant differences between subjects with M- and non-M-shaped vertical ground reaction forces with regard to timed up and go, functional reach test and Japan Orthopaedic Association score. There were also significant differences between the 2 groups (M shaped and non-M-shaped) in gait parameters.

Conclusion: Evaluation of the vertical ground reaction force to determine its shape may be a useful and simple tool in the analysis of gait and functional performance.

Key words: knee pain, gait analysis, elderly females, ground reaction force, osteoarthritis.

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Correspondence address: Toshiaki Takahashi, Department of Orthopaedic Surgery, Kochi Medical School, Oko-cho, Nankoku, Kochi, 783-8505, Japan. E-mail: takahast@kochi-ms.ac.jp

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INTRODUCTION

Osteoarthritis of the knee is one of the most common diseases in elderly females. There are several ways of testing locomotor function of the lower extremity, including measures of muscle strength, gait analysis and some types of knee evaluation scales (1–3). However, there is limited evidence that these parameters

are highly correlated with the functional state of the knee. Gait analysis is becoming recognized as an important clinical tool in orthopaedics, in pre-surgery planning, post-surgery monitoring and in a posterior evaluation of various corrective interventions (4, 5). However, it is sometimes difficult for clinicians to analyse the large amounts of data gathered in the assessment of gait time and distance parameters (5).

Objective quantitative assessment of mobility and balance is important for older people because problems with gait and balance can result in a restriction of activity. The Timed Up and Go (TUG) test correlates with gait speed, balance and movement of the lower extremities (6). The Functional Reach (FR) test is a simple measurement of standing balance that can predict falls in elderly people (7, 8).

There have been several reports concerning gait analysis in osteoarthritis of the knee (1, 9). The vertical ground reaction force (VGRF) has been shown to be a reliable and repeatable feature of gait (10–11). There have been numerous studies regarding ground reaction forces during walking (12–14). Gait speed significantly affects VGRF (12, 13, 16). The VGRF varies continually from the instant of initial contact until the foot leaves the supporting surface (17). Body mass, proportions, walking style and balance all affect VGRF (17).

There have been only a few reports regarding the relationship between VGRF and various gait parameters in elderly females with osteoarthritic knees. Analyses that include a classification of VGRF have also been limited. Thus, in this study, we focused on the vertical ground force component, classified into 2 groups: M-shaped, also known as a “dual-hump” shape (18) and non-M-shaped. The purpose of this study was to evaluate the relationship between knee pain and various indicators of the combined performance of the leg, including gait parameters, functional performance, TUG and FR and to determine whether the classification of VGRF is correlated with gait parameters and functional performance.

MATERIAL AND METHODS

Subjects

We defined the subjects with osteoarthritic knee as having knee pain and less than 100 points of Japan Orthopaedic Association (JOA) score. We have been performing annual medical checks of adults aged 65 years and

Table I. Japan Orthopaedic Association scores based on the osteoarthritic knee evaluation form

	Score
<i>Pain on walking (maximum 30 points)</i>	
No pain, walking unlimited	30
Pain, walking unlimited	25
Pain, walking distance of 0.5-1 km	20
Pain, walking less than 0.5 km	15
Pain, walking only indoors	10
Cannot walk	5
Cannot stand	0
<i>Pain on ascending or descending stairs (maximum 25 points)</i>	
No pain	25
Pain, relieved by using handrails	20
Pain, with handrails, but no pain with each step	15
Pain, with each step, pain relieved by using handrails	10
Pain, with each step even with handrail use	5
Cannot ascend or descend	0
<i>Range of motion (maximum 35 points)</i>	
Kneeling	35
Sideways or cross-legged sitting	30
More than 110°	25
75°-109°	20
35°-74°	10
Less than 35°	0
<i>Joint effusion (maximum 10 points)</i>	
No effusion	10
Occasional puncture required	5
Frequent puncture required	0
Maximum total points	100

over who live in the community in Kahoku of Kochi prefecture since 1994. We then examined the locomotor ability of the subjects.

The mean age of the 130 participants was 80 years (range 65-94 years), with a mean height of 143.0 cm. Knee pain while walking was classified into 3 groups: no pain (45%), unilateral pain (28%) or bilateral pain (26%).

Average maximum flexion for all subjects was 140.9 ± 13.4 degrees. Average maximum extension was 5.2 ± 6.1 degrees. JOA scores determined from the osteoarthritic knee evaluation form (Table I) were used for the evaluation of knee function (19). JOA (0-100 points) scores averaged 90.1 ± 12.9 points. The distance between the medial chondyles was evaluated, and averaged 2.5 ± 1.4 fingers breadth.

Co-morbidities of the subjects included hypertension (31.6%), cardiac arrhythmia (6.1%), coronary artery disease (3.2%) and diabetes mellitus (5.7%). Eighteen subjects with the following conditions were excluded from this study: knee disorders after total knee arthroplasty (5 patients), high tibial osteotomy (2 patients), miscellaneous knee operations (2 patients), osteosynthesis (1 patient), multiple cerebral infarctions (7 patients) and Parkinson's disease (1 patient).

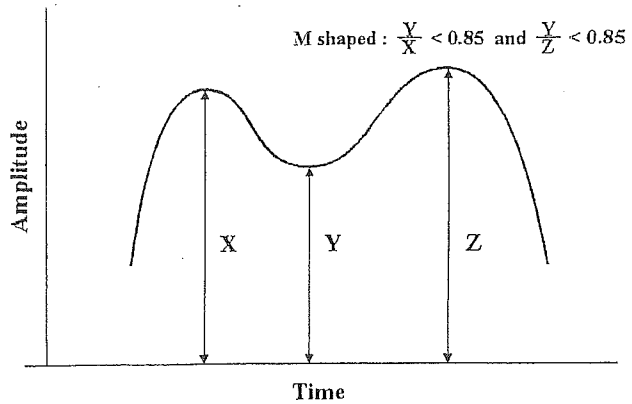


Fig. 1. Calculation of M-wave shape of vertical ground reaction force. M-shaped was defined as Y/X and Y/Z less than 0.85. All others were defined as non-M-shaped.

Gait analysis

The interviewer asked to record the gait parameters of subjects who were able to walk a distance of 10 metres. Subjects were allowed to wear their usual clothes and use their preferred (normal) speed while walking a 7-metre-long course. The first and last 2-3 metres on the walkway were not considered for measurement.

A Gait Scan® 8000 (Nitta Co. Ltd, Osaka, Japan) of gait-pattern measurement system consisting of a thin-film sensor walkway, a computer for automatic recording of the data was used in this study. This gait analysis device consists of a sensor seat (264 × 52 cm), a connector unit which fixes the sensor seat, and an interface board with a personal computer and software for data analysis.

Gait parameters, temporal distance and time factors, and ground reaction forces were measured simultaneously. Ground reaction force data for both legs was collected at a self-selected walking speed. The peak force was measured as the highest VGRF that occurred anytime during the stance phase, while the lowest VGRF occurred during the mid-stance phase.

Patients were classified into 2 groups based on the VGRF: M-shaped and non-M-shaped (Fig. 1). We defined M-shaped as lowest/highest × 100 (%) of less than 85. We assessed the shape of the VGRF for every step and classified individuals based on the result that was obtained for the greater number of steps. The mean gait variables measured in this study were walking speed (metres/sec), stride length, step width (cm), time of stride, time of single stance and time of double stance (sec). The distance parameters of stride length and step width were normalized for the height of the subject (15).

Functional performance

Timed up and go

To measure TUG, subjects were given oral instructions to stand up from

Table II. Data (mean (SD)) for patients without pain, with unilateral and bilateral pain in elderly females

	No pain (n = 59)	Unilateral pain (n = 37)	Bilateral pain (n = 34)
Body weight (kg)	45.2 (7.53)	47.2 (7.49)	52.2 (8.94)
Timed up and go (sec)	13.0 (3.0)	13.8 (4.51)	15.1 (7.28)
Functional reach (cm)	20.6 (7.2)	21.0 (7.07)	23.1 (6.89)
Stride length (cm)	63.2 (9.21)	61.1 (11.7)	61.7 (10.9)
Stride width (cm)	5.4 (2.20)	5.7 (2.14)	5.6 (1.92)
Time of stride (sec)	1.1 (0.117)	1.1 (0.179)	1.2 (0.167)
Time of single stance (sec)	0.58 (0.059)	0.59 (0.073)	0.60 (0.082)
Time of double stance (sec)	0.16 (0.037)	0.17 (0.052)	0.18 (0.069)
Gait speed (m/s)	0.6 (0.115)	0.56 (0.147)	0.54 (0.135)

Table III. Participant characteristics given as mean (SD)

	Height (cm)	Weight (kg)	JOA (point)	TUG (sec)	FR (cm)
Right side					
M-shaped (n = 32)	143.8 (7.2)	46.1 (8.6)	95.2 (10.3)	11.6 (2.3)	22.5 (6.9)
Non-M-shaped (n = 47)	142.4 (5.2)	45.9 (7.4)	86.6 (13.5)	14.6 (4.5)	18.4 (8.2)
	p = 0.187	p = 0.96	p = 0.0013	p < 0.0001	p = 0.026
Left side					
M-shaped (n = 29)	143.1 (8.1)	45.8 (8.1)	96.9 (6.25)	11.35 (2.25)	22.9 (7.56)
Non-M-shaped (n = 50)	142.9 (4.7)	46.2 (7.8)	86.1 (14.1)	14.5 (4.44)	18.45 (7.74)
	p = 0.41	p = 0.92	p = 0.0002	p < 0.0001	p = 0.026

JOA: Japan Orthopaedic Association; TUG: timed up and go; FR: functional reach

a chair, walk 3 metres as quickly and as safely as possible, cross a line marked on the floor, turn around, walk back and sit down (6).

Functional reach. FR represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position (7, 20).

Statistics

Data were expressed as a mean and standard deviation (SD). Differences between groups were evaluated using a Kruskal Wallis test for the analysis of knee pain (Table II) and a Mann-Whitney U test for the analysis of VGRF (Tables III and IV). Statistical significance was set at $p < 0.05$.

RESULTS

Occurrence of knee pain showed a significant association with body weight; however, there was no significant difference between patients with or without pain and TUG, FR, or any gait parameters (Table II).

The shape of the VGRF was associated with certain measures of functional performance, as well as the JOA score (Table III). Patients exhibiting an M-shaped VGRF on the right and left sides had shorter TUGs and longer FRs than patients with a non-M-shaped VGRF. The total JOA score was greater for the M-shaped group than for the non-M-shaped group. Within both groups, the ground reaction forces were similar on left and right sides.

Several gait parameters varied according to the shape of the VGRF (Table IV). Stride length was longer for the M-shaped VGRF group than for the non-M-shaped VGRF group. The times of stride and single and double stance were shorter in the M-shaped VGRF group than in the non-M-shaped group. The

walking speed of the M-shaped group was faster than that of the non-M-shaped group. There was no significant difference between the 2 groups in the step width on both sides.

DISCUSSION

Osteoarthritis of the knee is common in elderly females and it is well-known that it is associated with gait disturbances. There have been numerous reports regarding the relationship between osteoarthritis and gait parameters. An evaluation of the relationship between gait parameters and knee pain in elderly females found no significant association between knee pain and gait parameters or functional performance. Findings such as these have suggested that numerous factors, such as the posture of the trunk, lumbar lesions, the condition of other joints (such as the hip and ankle) and mental status, all contribute to gait parameters in elderly females. Therefore, it is important to consider these factors in the analysis of people with knee pain.

An advantage of gait analysis as a diagnostic or research tool is that many factors can be assessed at one time; however, proper evaluation of the resulting data can be complex. Quantitative data of time and distance parameters of gait analysis is difficult to understand and interpret whether it is within normal or not.

One study showed no overall abnormality in the shape or amplitude of the ground reaction force measured for the natural gait of knee-pain subjects (21). The present study, which involved the evaluation of one simple aspect of the VGRF (classified as M-shaped and non-M-shaped), showed that the shape of the ground reaction force was correlated with the pain

Table IV. Gait parameters (mean (SD)) for subjects with M-shape and non-M-shape of vertical ground reaction force

	Stride length (cm)	Step width (cm)	Time of stride (sec)	Time of single stance (sec)	Time of double stance (sec)	Gait speed (m/s)
Right side						
M-shaped (n = 32)	70.1 (8.7)	5.5 (2.1)	1.03 (0.09)	0.5 (0.04)	0.1 (0.02)	0.7 (0.11)
Non-M-shaped (n = 47)	55.8 (8.9)	5.8 (2.3)	1.2 (0.15)	0.6 (0.07)	0.2 (0.047)	0.5 (0.1)
	p < 0.0001	p = 0.712	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
Left side						
M-shaped (n = 29)	70.6 (9.2)	5.5 (2.08)	1.0 (0.087)	0.54 (0.042)	0.1 (0.02)	0.69 (0.12)
Non-M-shaped (n = 50)	56.5 (9.9)	6.0 (2.47)	1.8 (0.15)	0.61 (0.075)	0.2 (0.046)	0.5 (0.11)
	p < 0.0001	p = 0.146	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001

component of the JOA score. In another study, increased gait speed was associated with shorter force periods and larger peak forces (16).

In the present study we found that there were no differences between the right and left legs with respect to gait parameters, functional performance or the shape of the ground reaction force. Consistent with our findings, another study showed no significant differences between the right and left foot with respect to ground reaction force during walking (22).

In our study we found that both gait parameters and functional performance were significantly correlated with the shape of the VGRF. Several previous studies have examined VGRFs in normal subjects and patients with osteoarthritis; however, prior to the present study, there was little known concerning the relationship between the VGRF and gait parameters or functional performance in elderly females with knee osteoarthritis. In one study it was found that the 2 peaks in the vertical component measured for the affected side in knee-osteoarthritis patients became less apparent, with significantly lower magnitudes than in normal subjects (18). In addition, patterns of VGRFs were nearly identical during overground and treadmill walking (23) and the general waveform and its characteristic features did not seem to be affected by the sex of normal subjects (18). In the present study, we could not find a correlation between pain and the mechanism of the shape of VGRF. Further study is needed to clarify the changing mechanism of VGRF in osteoarthritic knee.

In the present study, we did not examine inter-rater reliability: future study is needed to investigate this and the validity with respect to M-shape and gait analysis.

In conclusion, our classification of VGRF is a simple and useful tool for assessment of gait function. It was correlated with many parameters of gait and functional performance, such as TUG and functional reach. Our study indicated that a change in the VGRF, from non-M-shaped to M-shaped, is crucial to the improvement of gait parameters and gait performance. Further studies are needed to seek methods for altering the shape of the ground reaction force.

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REFERENCES

- Murray MP, Gore DR, Sepic SB, Mollinger LA. Antalgic maneuvers during walking in men with unilateral knee disability. *Clin Orthop* 1985; 199: 192-200.
- Prince F, Corriveau H, Hebert R, Winter DA. Gait in the elderly. *Gait Posture* 1997; 5: 128-135.
- Stauffer RN, Chao EYS, Gyory AN. Biomechanical gait analysis of the diseased knee joint. *Clin Orthop* 1977; 126: 246-255.
- Kaufman KR, Sutherland DH. Future trends in human motion analysis. In: Harris GF, Smith PA, eds. *Human motion analysis. Current applications and future directions*. New York: IEEE Press; 1996, p. 187-215.
- Bertani A, Cappello A, Benedetti MG, Simoncini L, Catani F. Flat foot functional evaluation using pattern recognition of ground reaction data. *Clin Biomech* 1999; 14: 484-493.
- Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; 39: 142-148.
- Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol* 1990; 45: 192-197.
- Weiner DK, Duncan PW, Chandler J, Studenski SA. Functional reach: a marker of physical frailty. *J Am Geriatr Soc* 1992; 40: 203-207.
- Goh JC, Bose K, Khoo BC. Gait analysis study on patients with varus osteoarthritis of the knee. *Clin Orthop* 1993; 294: 223-231.
- Kadaba MP, Ramakrishnan HK, Wootten ME, Gainey J, Gorton G, Cochran GVB. Repeatability of kinematic, kinetic, and electromyographic data in normal adult gait. *J Orthop Res* 1989; 7: 849-860.
- Olsson E, Oberg K, Ribbe T. A computerized method for clinical gait analysis of floor reaction forces and joint angular motion. *Scand J Rehabil Med* 1986; 18: 93-99.
- Andriacchi TP, Ogle JA, Galante JO. Walking speed as a basis for abnormal gait measurements. *J Biomech* 1977; 10: 261-268.
- Alexander RM, Jayes AS. Fourier analysis of forces exerted in walking and running. *J Biomech* 1980; 13: 383-390.
- Balmaseda MT, Koozekanani SH, Fatehi MT, Gordon C, Dreyfuss PH, Tanbonlinog BC. Ground reaction forces, center of pressure, and duration of stance with and without an ankle-foot orthosis. *Arch Phys Med Rehabil* 1988; 69: 1009-1112.
- Chao EY, Laughman RK, Schneider E, Stauffer RN. Normative data of knee joint motion and ground reaction forces in adult level walking. *J Biomech* 1983; 16: 219-233.
- Nilsson J, Thorstensson A. Ground reaction forces at different speeds of human walking and running. *Acta Physiol Scand* 1989; 136: 217-227.
- Cook TM, Farrell KP, Carey IA, Gibbs JM, Wiger GE. Effects of restricted knee flexion and walking speed on the vertical ground reaction force during gait. *J Orthop Sports Phy Ther* 1997; 25: 236-244.
- Schneider E, Chao EY. Fourier analysis of ground reaction forces in normals and patients with knee joint disease. *J Biomech* 1983; 16: 591-601.
- Takahashi T, Wada Y, Tanaka M, Iwagawa M, Ikeuchi M, Hirose D, Yamamoto H. Dome-shaped proximal tibial osteotomy using percutaneous drilling for osteoarthritis of the knee. *Arch Orthop Trauma Surg* 2000; 120: 32-37.
- Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T. Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. *J Am Geriatr Soc* 1996; 44: 569-572.
- Radin EL, Yang KH, Riegger C, Kish VL, O'Connor JJ. Relationship between lower limb dynamics and knee joint pain. *J Orthop Res* 1991; 9: 398-405.
- Herzog W, Nigg BM, Read LJ, Olsson E. Asymmetries in ground reaction force patterns in normal human gait. *Med Sci Sports Exerc* 1989; 21: 110-114.
- White SC, Yack HJ, Tucker CA, Lin HY. Comparison of vertical ground reaction forces during overground and treadmill walking. *Med Sci Sports Exerc* 1998; 30: 1537-1542.

LETTERS TO THE EDITOR

EFFECTS OF PHYSICAL EXERCISE ON PLASMA CONCENTRATIONS OF SEX HORMONES IN ELDERLY WOMEN WITH DEMENTIA

To the Editor: Physical exercise may slow the functional decline in elderly people and has been associated with a low incidence of dementia.¹ Physical activities have shown favorable effects on cognitive function as well as on neuropsychiatric symptoms and behavioral disturbance in demented subjects,^{1,2} the mechanism of which is currently unknown. Because low plasma levels of sex hormones have been implicated in dementia,³ it is reasonable to hypothesize that physical exercise could elevate plasma sex hormone levels. Here, we report a preliminary study in which daily physical exercise for 3 months increased the plasma levels of sex hormones, including dehydroepiandrosterone (DHEA) and testosterone, in elderly women with dementia. Thirteen women (aged 74–91, mean age \pm standard deviation 84 ± 5) living in group homes for the elderly (small-scale facilities providing communal living) located in Nagano Prefecture, Japan, were enrolled. They were diagnosed as having Alzheimer's disease according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, but did not have malnutrition, malignancy, or endocrine disease. Blood sampling and functional assessment were performed at baseline, at the end of a 3-month exercise program, and at the end of a 3-month follow-up period, during which the subjects returned to ordinary sedentary living. The exercise program consisted of stretching and mild resistance training using a chair and a 0.5-kg weight. The exercise was performed as a group, with training for 30 minutes daily under the instruction of a physical therapist twice a week and by other caregiver staff five times a week. Care other than exercise was comparable throughout the study. Fasting blood samples were collected early in the morning before exercise. A commercial laboratory determined plasma levels of estradiol, testosterone, DHEA, DHEA sulfate, and sex hormone-binding globulin, in addition to blood cell counts and blood chemical parameters.

Basic activities of daily living (ADLs) were assessed using the Barthel Index and cognitive function using the Mini-Mental State Examination.

At baseline, the subjects showed moderate cognitive impairment and dependency and relatively low sex hormone levels (Table 1). After 3 months of exercise, significant increases were found in plasma levels of testosterone of 18%, estradiol of 38%, and DHEA of 37%, all of which returned to the baseline levels 3 months after cessation of the exercise program. A similar alteration was found in plasma DHEA sulfate level, but the increase by exercise was not statistically significant (mean \pm standard error 452 ± 62 ng/mL at baseline, 508 ± 72 ng/mL after exercise, and 464 ± 77 ng/mL after discontinuation. Sex hormone-binding globulin, albumin, and other blood parameters did not change throughout the study (Table 1 and data not shown). Despite the increases in sex hormones after the exercise program, neither Barthel Index nor Mini-Mental State Examination scores changed significantly during the study.

Previous studies^{4,5} have shown stimulatory effects of endurance or resistance exercise on circulating hormones in healthy postmenopausal women; metabolic alterations and increased blood flow of endocrine organs via nitric oxide and cyclic adenosine monophosphate production may play a causal role, but hormonal responses in frail or demented women have not been examined. In the present study, plasma levels of estradiol, testosterone, and DHEA were higher after 3 months of physical exercise in elderly women with dementia, whereas cognitive function and basic ADLs did not improve. Given the protective effect of exercise and sex hormones on cognitive impairment, a control sedentary group should be included to examine whether this exercise program might delay cognitive decline. Nevertheless, the finding that exercise can increase plasma sex hormone levels in demented women provides a mechanistic insight into the effect of exercise or physical activities on cognitive impairment. The results of this preliminary study need to be confirmed using larger randomized, controlled trials with longer follow-up periods.

Table 1. Effects of Daily Physical Exercise on Plasma Concentrations of Sex Hormones in Elderly Women with Dementia (N = 13)

Measurement	Baseline	Exercise (3 Months)	Discontinuation (3 Months)
	Mean \pm Standard Error of the Mean		
Testosterone, ng/dL	51.4 \pm 3.3	60.8 \pm 3.3 [†]	47.9 \pm 3.9
Estradiol, pg/mL	15.2 \pm 1.2	21.0 \pm 1.2 [†]	19.4 \pm 2.9
Dehydroepiandrosterone, ng/mL	1.84 \pm 0.29	2.52 \pm 0.41 [*]	1.95 \pm 0.27
Sex hormone binding globulin, nmol/L	75.0 \pm 6.1	69.1 \pm 8.1	68.3 \pm 8.3
Barthel Index	75.0 \pm 5.4	70.0 \pm 7.1	66.5 \pm 9.4
Mini-Mental State Examination score	13.9 \pm 1.9	13.8 \pm 2.0	12.4 \pm 2.5

P < .05; [†].01 versus baseline using paired t test.

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Masahiro Akishita, MD
Shizuru Yamada, MD
Hiromi Nishiya, MD
Kazuki Sonohara, MD
Ryuhei Nakai, MD
Kenji Toba, MD

Department of Geriatric Medicine
Kyorin University School of Medicine
Tokyo, Japan

REFERENCES

1. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* 2003;14:125-130.
2. Cummings JL. Alzheimer's disease. *N Engl J Med* 2004;351:56-67.
3. Almeida OP, Barclay L. Sex hormones and their impact on dementia and depression: A clinical perspective. *Expert Opin Pharmacother* 2001;2:527-535.
4. Copeland JL, Consitt LA, Tremblay MS. Hormonal responses to endurance and resistance exercise in females aged 19 to 69 years. *J Gerontol A Biol Sci Med Sci* 2002;57A:B158-B165.
5. Kemmler W, Wildt L, Engelke K et al. Acute hormonal responses of a high impact physical exercise session in early postmenopausal women. *Eur J Appl Physiol* 2003;90:199-209.

Inhibitory effect of low-dose estrogen on neointimal formation after balloon injury of rat carotid artery

Tokumitsu Watanabe^a, Yukiko Miyahara^a, Masahiro Akishita^b, Takashi Nakaoka^c, Naohide Yamashita^c, Katsuya Iijima^a, Hong Kim^a, Koichi Kozaki^a, Yasuyoshi Ouchi^{a,*}

^aDepartment of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

^bDepartment of Geriatric Medicine, Kyorin University School of Medicine, Tokyo 181-8611, Japan

^cDepartment of Advanced Medicine, Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan

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Abstract

The current regimens of hormone replacement therapy for postmenopausal women, estrogen combined with progestogen, have failed to show beneficial effects for the prevention of atherosclerotic disease. Although the relatively higher dose of estrogen contained in those regimens exerted adverse effects, there are few data examining a lower dose of estrogen in an atherosclerosis model. Therefore, we investigated experimentally whether lower doses of estrogen could inhibit neointimal formation after balloon injury of the rat carotid artery. Ten-week-old Wistar rats were subjected to ovariectomy or sham-operation ($n=7$). Four days after ovariectomy, rats were implanted with an osmotic mini-pump containing 17- β estradiol (0.2, 1, 2, 10 and 20 $\mu\text{g}/\text{kg}/\text{day}$; $n=6, 4, 8, 6$ and 5, respectively) or placebo ($n=10$). After 3 days of hormone therapy, balloon injury was performed in the left common carotid artery. Neointimal formation was histologically evaluated 2 weeks after injury. Cross-sectional intimal area and the ratio of intimal area to medial area were dose-dependently reduced by estrogen replacement compared with those in ovariectomized rats without estrogen replacement. The effects of estrogen replacement were identical to those of an angiotensin II type 1 receptor blocker, candesartan. Interestingly, the effect was significant even in rats receiving lower doses of estrogen, in which plasma estradiol concentrations were not increased and the hyperplastic response of the uterus was minimal. These results suggest the efficacy of low-dose estrogen therapy for the protection of atherosclerosis.

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Keywords: Estrogen; Low-dose; Neointimal formation

1. Introduction

Previous studies have shown that estrogen administration in ovariectomized animals inhibits the process of atherosclerosis. Different doses of estrogens in combination with or without progestins have decreased the lesion formation in injured vessels or cholesterol-fed animals using rodents, rabbits and swine (Chen et al., 1996; Oparil et al., 1997; Bakir et al., 2000; Chandrasekar and Tanguay, 2000; Finking et al., 2001; Tolbert et al., 2001). Most of the

studies, however, have used the estradiol doses of 20 $\mu\text{g}/\text{kg}/\text{day}$ or higher, which were accompanied by the raised plasma estradiol concentration compared to intact female animals (Chen et al., 1996; Bakir et al., 2000; Tolbert et al., 2001). More importantly, these doses of estrogen (≥ 20 $\mu\text{g}/\text{kg}/\text{day}$ of estradiol subcutaneously) elicited adverse effects such as uterine hyperplasia (Bakir et al., 2000; Tolbert et al., 2001; Xu et al., 2003) and dyslipidemia (Joles et al., 1998; Gades et al., 1998; Tomiyoshi et al., 2002). On the other hand, it has been reported that the effect of estradiol on uterine weight was dose-dependent (Kerdelhue and Jolette, 2002) and that low dose estrogen (approximately 3 $\mu\text{g}/\text{kg}/\text{day}$ of estradiol) could exert its favorable effect on bone metabolism (Chen et al., 2001). Since limited information is

* Corresponding author. Tel.: +81 3 5800 8830; fax: +81 3 5800 6530.
E-mail address: youchi-ky@umin.ac.jp (Y. Ouchi).

available on the vascular effect of low dose estrogen therapy, it is intriguing to study whether the lower dose of estrogen could inhibit vascular lesion formation.

In the present study, we hypothesized that lower doses of estrogen could have protective effects on the process of atherosclerosis with minimal adverse effects. To test this hypothesis, we examined neointimal formation of the carotid artery after balloon angioplasty in ovariectomized female rats receiving 10 µg/kg/day or lower doses of estradiol.

2. Materials and methods

2.1. Animals

Ten-week-old female Wistar rats (Oriental Yeast, Tokyo) were used in this study. They were housed in individual cages in a room in which lighting was controlled (12 h on, 12 h off) and room temperature was kept at ≈ 22 °C. They were given a standard diet and water ad libitum. All the surgical procedures were performed under sterile conditions. All of the experimental protocols were approved by the Animal Research Committee of the University of Tokyo.

2.2. Experimental protocols

Rats were randomly divided into 10 groups. Nine groups of rats were subjected to ovariectomy and the other group underwent sham operation (Akishita et al., 1997). After a 4-day recovery period, six groups of ovariectomized rats were subcutaneously implanted with osmotic minipumps (Alzet 2002, 0.5 µl/h; Alza) prefilled with water-soluble 17β-estradiol (0.2, 1, 2, 10 or 20 µg/kg/day; Sigma) or its vehicle (2-hydroxypropyl-β-cyclodextrin; Sigma) under ether anesthesia. To compare the effect of estrogen with that of an angiotensin II type 1 (AT1) receptor blocker, candesartan, the remaining four groups of rats were subcutaneously implanted with an osmotic minipump containing the active metabolite of candesartan, candesartan cilexetil (2, 20 or 200 µg/kg/day; kindly donated by Takeda Chemical Industries, Tokyo) or its vehicle (0.9% saline).

Three days after minipump implantation, balloon injury was performed as previously described (Chen et al., 1996; Nakaoka et al., 1997). General anesthesia was induced by the administration of 90 mg/kg of ketamine intraperitoneally and 15 mg/kg of xylazine intramuscularly. The left carotid artery was exposed and its branches were ligated using 7-0 nylon. After intravenous injection of 75 U/kg of heparin, a portion of the external carotid artery and a portion of the internal carotid artery were cross-clipped using a microclip (2v-clip: S&T, Neuhausen, Switzerland). A 2F Fogarty embolectomy catheter (Baxter, Irvine, CA) was introduced into the artery via the external carotid

artery. The common carotid artery was injured by six passes of an embolectomy catheter inflated with 0.2 ml of air. The portion proximal to the incision was ligated with 7-0 nylon, the cross-clip was released and the common carotid artery was reperfused.

2.3. Measurement of hormones and lipids

Blood sampling was performed at sacrifice, after a 16-h overnight fast, to measure serum concentrations of estradiol and progesterone, serum lipids and other biochemical parameters. Serum estradiol, estrone and progesterone concentrations were measured by sensitive radioimmunoassay (Hashimoto et al., 2002). Serum total cholesterol and triglyceride concentrations were measured enzymatically, and serum high-density lipoprotein cholesterol concentration was measured by heparin-Ca²⁺ Ni²⁺ precipitation method (Hashimoto et al., 2002).

2.4. Morphometrical analysis of the balloon-injured carotid artery

A portion of the left common carotid artery was harvested at 14 days after balloon injury. The artery was perfusion- and pressure-fixed at 100 mm Hg using 10% neutral formalin buffer and then paraffin-embedded. Five round cross-sections per 1.5-cm length of artery specimens were stained with *Elastica van Gieson staining*, and photographed. Cross-sectional areas of the intima and the media were measured using an image analyzing software package (Scion Image, shared NIH software). The average of five sections was used for analysis as the value of each animal.

2.5. Data analysis

Values are expressed as mean ± S.E.M. in the text, table and figures. Data were analyzed by one-factor analysis of variance (ANOVA) followed by Newman-Keuls' multiple comparison test. Differences with a value of $P < 0.05$ were considered statistically significant.

3. Results

Sixty-five rats were set up and allocated to each group. Four rats were excluded because of failure of intervention. Estrogen replacement in ovariectomized rats increased serum concentration of estradiol dose-dependently, and replacement of 2 µg/kg/day estradiol achieved a concentration comparable to that in sham-operated rats (Table 1). In all groups, the serum concentration of estrone was below the detection limit (data not shown) and that of progesterone was unchanged. With respect to the lipid profile, the concentration of total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol were increased in rats

Table 1

Blood pressure, serum lipids, plasma hormone concentrations and body and uterus weight after balloon injury of left carotid arteries of female Wistar rats

	Sham	Ovariectomy+17 β -estradiol (μ g/kg/day)						Ovariectomy+TCV-116 (μ g/kg/day)		
		0	0.2	1	2	10	20	0	2	20
No. of rats	7	10	6	4	8	6	5	4	4	4
SBP (mm Hg)	121 \pm 4	113 \pm 7	123 \pm 2	120 \pm 5	127 \pm 2	121 \pm 4	121 \pm 4	121 \pm 7	122 \pm 7	116 \pm 8
T.chol (mg/dl)	76 \pm 9	75 \pm 5	86 \pm 4	78 \pm 10	84 \pm 6	96 \pm 5 ^a	113 \pm 3 ^b	79 \pm 2	89 \pm 4	81 \pm 8
HDL-C (mg/dl)	20 \pm 2	21 \pm 3	20 \pm 2	16 \pm 3	23 \pm 2	27 \pm 1	30 \pm 1 ^a	17 \pm 2	21 \pm 2	22 \pm 2
Triglyceride (mg/dl)	41 \pm 6	53 \pm 8	46 \pm 9	64 \pm 16	91 \pm 13 ^a	87 \pm 10 ^a	153 \pm 31 ^b	64 \pm 11	25 \pm 6	35 \pm 10
Estradiol (pg/ml)	19 \pm 4 ^b	8 \pm 1	9 \pm 1	12 \pm 2	20 \pm 2 ^b	54 \pm 5 ^b	96 \pm 3 ^b	11 \pm 3	11 \pm 1	14 \pm 2
Progesterone (ng/ml)	20 \pm 5	13 \pm 2	6 \pm 3	21 \pm 5	9 \pm 2	11 \pm 3	5 \pm 2	16 \pm 4	21 \pm 6	15 \pm 2
Body weight (g)	269 \pm 6	282 \pm 8	281 \pm 8	260 \pm 6	264 \pm 6	257 \pm 5 ^a	263 \pm 7	285 \pm 10	290 \pm 5	290 \pm 3
Uterus (mg)	661 \pm 102 ^b	174 \pm 29	321 \pm 23	577 \pm 46 ^b	511 \pm 76 ^b	–	–	148 \pm 22	149 \pm 5	156 \pm 7

Values are expressed as mean \pm S.E.M. SBP, systolic blood pressure; T.chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; –, not examined.

^a P <0.05 vs. OVX+0 μ g/kg/day of 17 β -estradiol.

^b P <0.01 vs. OVX+0 μ g/kg/day of 17 β -estradiol.

receiving higher doses of estrogen, as previously reported (Gades et al., 1998; Joles et al., 1998; Tomiyoshi et al., 2002), whereas those were unchanged in rats receiving 2 μ g/kg/day or a lower dose of estrogen. The body weight of rats treated with higher doses was significantly lower than that in rats without estrogen replacement. In contrast, uterine weight in rats receiving lower doses of estrogen was greater than that in rats without estrogen.

Morphometric analysis showed that the neointimal area of the carotid artery was dose-dependently decreased by estrogen replacement (Figs. 1 and 2). As shown in Fig. 2, neointimal formation was sufficiently attenuated even in rats treated with 0.2 μ g/kg/day of estradiol compared to that in ovariectomized rats without estrogen replacement. The inhibitory effect of estrogen on neointimal formation

was compared with that of candesartan because the effects of AT1 receptor blockers including candesartan have been established (Kim et al., 2002; Liu et al., 2002; Nozawa et al., 1999; Tazawa et al., 1999). The effect of 20 μ g/kg/day estradiol was more potent than that of subdepressor dose of candesartan (20 μ g/kg/day) and was as potent as that of 200 μ g/kg/day candesartan; a dose that lowered blood pressure and body weight as well as neointimal formation (intima/media ratio was 0.66 \pm 0.07, data not shown). Importantly, the effect of 2 μ g/kg/day or a lower dose of estradiol on neointima formation was comparable to that of 20 μ g/kg/day candesartan (Fig. 2). Medial area was not different among all groups of rats. Small non-significant differences in several measurements between the control for estrogen and that for candesartan were likely to be due

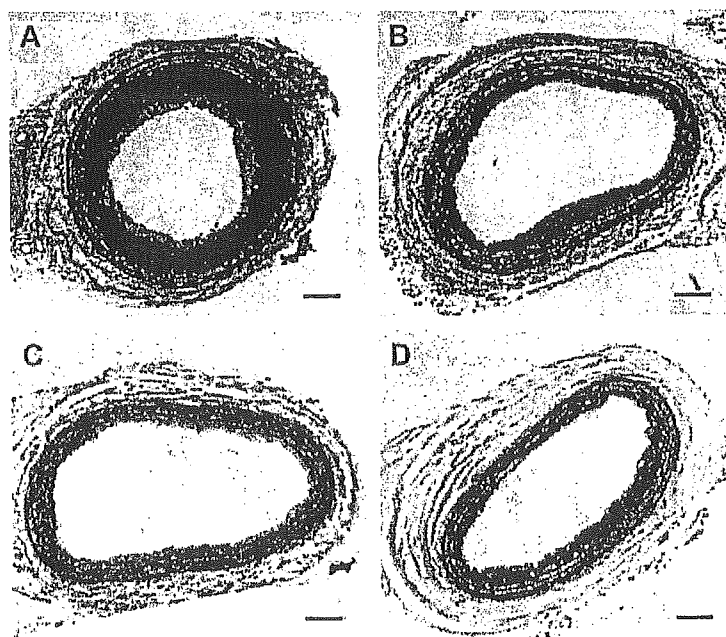


Fig. 1. Representative cross-sections of the rat carotid artery 2 weeks after balloon injury (elastica van gieson staining, magnification \times 100). Rats were treated with 20% cyclodextrin vehicle (A), 0.2 μ g/kg/day of 17- β estradiol (B), 20 μ g/kg/day of 17- β estradiol (C) and 20 μ g/kg/day of candesartan (D). Bars: 100 μ m.

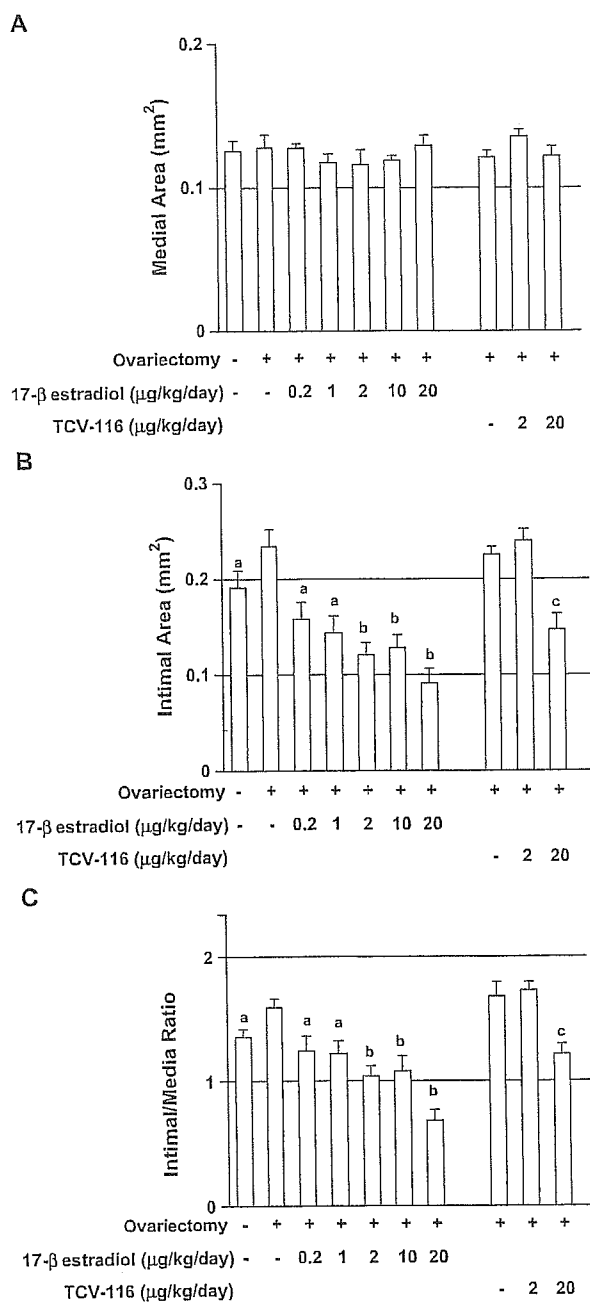


Fig. 2. Morphometric analyses of intimal area (A), medial area (B) and intima/media area ratio (C) in the carotid artery 2 weeks after balloon injury. The results are expressed as mean \pm S.E.M. ^a $P < 0.05$, ^b $P < 0.01$ vs. ovariectomized rats without 17- β estradiol, ^c $P < 0.01$ vs. ovariectomized rats without candesartan.

to the variation of the measurements rather than the effect of vehicle for each group.

4. Discussion

This study showed that subcutaneous administration of 2 μ g/kg/day or lower doses of estradiol inhibited neointimal

formation after vascular injury with minimal adverse effects on the uterus and lipid metabolism, suggesting the efficacy of lower doses of hormone replacement therapy for the prevention of atherosclerosis.

Estrogen has been reported to inhibit neointimal formation after vascular injury in rodents using balloon angioplasty of the rat carotid artery (Bakir et al., 2000; Chen et al., 1996; Oparil et al., 1997, 1999), cuff placement around the rat femoral artery (Akishita et al., 1997) and ligation of the mouse carotid artery (Tolbert et al., 2001). Oparil and her colleagues have shown using the rat carotid balloon-injury model that subcutaneous administration of 20 μ g/kg/day estradiol reduced neointimal formation by more than 50% compared to that without estradiol treatment (Chen et al., 1996; Oparil et al., 1997, 1999; Bakir et al., 2000). In their studies, plasma estradiol levels in estrogen-replaced rats (135.0 ± 5.7 pg/ml, Chen et al., 1996, or 32.0 ± 4.8 pg/ml, Bakir et al., 2000) were higher than those in intact female rats (51.9 ± 5.8 pg/ml, Chen et al., 1996, or 25 ± 6.9 pg/ml, Bakir et al., 2000). In the present study, administration of 10 or 20 μ g/kg/day estradiol in ovariectomized rats inhibited neointimal formation with the increased plasma estradiol concentration beyond that in sham-operated rats as well. These results suggest that the estradiol doses used in the previous studies (>10 μ g/kg/day) may be relatively high although plasma estradiol concentration fluctuates in rats with the estrous cycle (ranged from 16 ± 2 to 39 ± 7 pg/ml, Anisimov and Okulov, 1980, or from 1 ± 1 to 44 ± 15 pg/ml, Hawkins et al., 1975), and changes with development and age (Meijs-Roelofs et al., 1975). In contrast, replacement of 2 μ g/kg/day estradiol achieved serum estradiol concentrations comparable to those in sham-operated rats in the present study. Replacement of 1 μ g/kg/day or a lower dose of estradiol did not increase the serum estradiol concentration. However, the inhibition of neointimal formation was significant at the lower doses and was comparable to the effect of 20 μ g/kg/day of candesartan (Fig. 2). Moreover, 1 μ g/kg/day or a lower dose of estradiol did not increase the serum triglyceride concentration, and 0.2 μ g/kg/day of estradiol caused the minimal and non-significant increase of uterus weight. This could be a new finding with respect to the adverse effects on lipid profiles and uterus. Taken these findings together, a local effect of estrogen replacement on organs or cells was observed even if circulating estrogen was not elevated, providing some hints on determining the dose of hormone replacement therapy.

In the present study, we did not demonstrate the mechanisms by which estrogen inhibited neointimal formation. Previous reports have shown that re-endothelialization (White et al., 1997), preservation of endothelial survival (Sudoh et al., 2001) and function (White et al., 1997), inhibition of smooth muscle cell proliferation (Akishita et al., 1997) and inhibition of fibroblast proliferation and differentiation in the adventitia (Oparil et al., 1999) contribute to the effect of estrogen on the response to

vascular injury. Stimulation of nitric oxide synthesis as well as modulation of other vasoactive substances has been implicated in these effects, although activation of endothelial nitric oxide synthase may play a major role (Chambliss and Shaul, 2002). Further investigation is needed to elucidate the contribution and interaction of these factors in the effects of lower doses of estrogen on neointimal formation.

Recent randomized trials (Hulley et al., 1998; Rossouw et al., 2002) have suggested that hormone replacement therapy with the standard regimen should not be recommended for postmenopausal women. Improvement of the regimen, such as the dose, route (oral or subcutaneous) or schedule (continuous or cyclic), could resolve the adverse effects of hormone replacement therapy, although few data are currently available (Grodstein et al., 2000; Jick et al., 1996; Hashimoto et al., 2002; Wakatsuki et al., 2003, 2004). Direct comparisons of animal studies to clinical studies are inadequate because several major differences can be pointed including route of administration, duration of the treatment, cardiovascular risk profile of subjects and body fat distribution. However, our experimental result that lower doses of estrogen inhibited the response to vascular injury with relatively small adverse effects may imply the potential efficacy of low dose hormone replacement therapy in postmenopausal women.

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References

- Akishita, M., Ouchi, Y., Miyoshi, H., Kozaki, K., Inoue, S., Ishikawa, M., Eto, M., Toba, K., Orimo, H., 1997. Estrogen inhibits cuff-induced intimal thickening of rat femoral artery: effects on migration and proliferation of vascular smooth muscle cells. *Atherosclerosis* 130, 1–10.
- Anisimov, V.N., Okulov, V.B., 1980. Effect of ageing on concentration of estradiol in serum and the epidermal G2 chalone in vaginal mucosa of rats. *Exp. Gerontol.* 15, 87–91.
- Bakir, S., Mori, T., Durand, J., Chen, Y.F., Thompson, J.A., Oparil, S., 2000. Estrogen-induced vasoprotection is estrogen receptor dependent: evidence from the balloon-injured rat carotid artery model. *Circulation* 101, 2342–2344.
- Chambliss, K.L., Shaul, P.W., 2002. Estrogen modulation of endothelial nitric oxide synthase. *Endocr. Rev.* 23, 655–686.
- Chandrasekar, B., Tanguay, J.F., 2000. Local delivery of 17-beta-estradiol decreases neointimal hyperplasia after coronary angioplasty in a porcine model. *J. Am. Coll. Cardiol.* 36, 1972–1978.
- Chen, S.J., Li, H., Durand, J., Oparil, S., Chen, Y.F., 1996. Estrogen reduces myointimal proliferation after balloon injury of rat carotid artery. *Circulation* 93, 577–584.
- Chen, J.L., Yao, W., Frost, H.M., Li, C.Y., Setterberg, R.B., Jee, W.S.S., 2001. Bipedal stance exercise enhances antiresorption effects of estrogen and counteracts its inhibitory effect on bone formation in sham and ovariectomized rats. *Bone* 29 (2), 126–133.
- Finking, D., Krauss, N., Romer, S., Eckert, S., Lenz, C., Kamenz, J., Menke, A., Brehme, U., Hanke, H., 2001. 17beta-estradiol, gender independently, reduces atheroma development but not neointimal proliferation after balloon injury in the rabbit aorta. *Atherosclerosis* 154, 39–49.
- Gades, M.D., Stern, J.S., van Goor, H., Nguyen, D., Johnson, P.R., Kaysen, G.A., 1998. Estrogen accelerates the development of renal disease in female obese Zucker rats. *Kidney Int.* 53, 130–135.
- Grodstein, F., Manson, J.E., Colditz, G.A., Willett, W.C., Speizer, F.E., Stampfer, M.J., 2000. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann. Intern. Med.* 133, 933–941.
- Hashimoto, M., Miyao, M., Akishita, M., Hosoi, T., Toba, K., Kozaki, K., Yoshizumi, M., Ouchi, Y., 2002. Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. *Menopause* 9, 58–64.
- Hawkins, R.A., Freedman, B., Marshall, A., Killen, E., 1975. Oestradiol-17 beta and prolactin levels in rat peripheral plasma. *Br. J. Cancer* 32, 179–185.
- Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., Vittinghoff, E., 1998. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 280, 605–613.
- Jick, H., Derby, L.E., Myers, M.W., Vasilakis, C., Newton, K.M., 1996. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 348, 981–983.
- Joles, J.A., van Goor, H., Koornans, H.A., 1998. Estrogen induces glomerulosclerosis in albuminemic rats. *Kidney Int.* 53, 862–868.
- Kerdelhue, B., Jolette, J., 2002. The influence of the route of administration of 17beta-estradiol, intravenous (pulsed) versus oral, upon DMBA-induced mammary tumour development in ovariectomised rats. *Breast Cancer Res. Treat.* 73, 13–22.
- Kim, S., Izumi, Y., Izumiya, Y., Zhan, Y., Taniguchi, M., Iwao, H., 2002. Beneficial effects of combined blockade of ACE and AT1 receptor on intimal hyperplasia in balloon-injured rat artery. *Arterioscler. Thromb. Vasc. Biol.* 22, 1299–1304.
- Liu, H.W., Iwai, M., Takeda-Matsubara, Y., Wu, L., Li, J.M., Okumura, M., Cui, T.X., Horiuchi, M., 2002. Effect of estrogen and AT1 receptor blocker on neointima formation. *Hypertension* 40, 451–457. (discussion 448–450).
- Meijs-Roelofs, H.M., Uilenbroek, J.T., De Greef, W.J., De Jong, F.H., Kramer, P., 1975. Gonadotrophin and steroid levels around the time of first ovulation in the rat. *J. Endocrinol.* 67, 275–282.
- Nakaoka, T., Gonda, K., Ogita, T., Otawara-Hamamoto, Y., Okabe, F., Kira, Y., Harii, K., Miyazono, K., Takuwa, Y., Fujita, T., 1997. Inhibition of rat vascular smooth muscle proliferation in vitro and in vivo by bone morphogenetic protein-2. *J. Clin. Invest.* 100, 2824–2832.
- Nozawa, Y., Matsuura, N., Miyake, H., Yamada, S., Kimura, R., 1999. Effects of TH-142177 on angiotensin II-induced proliferation, migration and intracellular signaling in vascular smooth muscle cells and on neointimal thickening after balloon injury. *Life Sci.* 64, 2061–2070.
- Oparil, S., Levine, R.L., Chen, S.J., Durand, J., Chen, Y.F., 1997. Sexually dimorphic response of the balloon-injured rat carotid artery to hormone treatment. *Circulation* 95, 1301–1307.
- Oparil, S., Chen, S.J., Chen, Y.F., Durand, J.N., Allen, L., Thompson, J.A., 1999. Estrogen attenuates the adventitial contribution to neointima formation in injured rat carotid arteries. *Cardiovasc. Res.* 44, 608–614.
- Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J., 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 288, 321–333.

- Sudoh, N., Toba, K., Akishita, M., Ako, J., Hashimoto, M., Iijima, K., Kim, S., Liang, Y.Q., Ohike, Y., Watanabe, T., Yamazaki, I., Yoshizumi, M., Eto, M., Ouchi, Y., 2001. Estrogen prevents oxidative stress-induced endothelial cell apoptosis in rats. *Circulation* 6;103 (5), 724–729.
- Tazawa, S., Nakane, T., Chiba, S., 1999. Angiotensin II type 1 receptor blockade prevents up-regulation of angiotensin II type 1A receptors in rat injured artery. *J. Pharmacol. Exp. Ther.* 288, 898–904.
- Tolbert, T., Thompson, A., Bouchard, P., Oparil, S., 2001. Estrogen-induced vasoprotection is independent of inducible nitric oxide synthase expression. Evidence from the mouse carotid artery ligation model. *Circulation* 104, 2740–2745.
- Tomiyoshi, Y., Sakemi, T., Aoki, S., Miyazono, M., 2002. Different effects of castration and estrogen administration on glomerular injury in spontaneously hyperglycemic Otsuka Long–Evans Tokushima Fatty (OLETF) rats. *Nephron* 92, 860–867.
- Wakatsuki, A., Okatani, Y., Ikenoue, N., Shinohara, K., Watanabe, K., Fukaya, T., 2003. Effect of lower dose of oral conjugated equine estrogen on size and oxidative susceptibility of low-density lipoprotein particles in postmenopausal women. *Circulation* 108, 808–813.
- Wakatsuki, A., Ikenoue, N., Shinohara, K., Watanabe, K., Fukaya, T., 2004. Effect of lower dosage of oral conjugated equine estrogen on inflammatory markers and endothelial function in healthy postmenopausal women. *Arterioscler. Thromb. Vasc. Biol.* 24 (3), 571–576.
- White, C.R., Shelton, J., Chen, S.J., Darley-Usmar, V., Allen, L., Nabors, C., Sanders, P.W., Chen, Y.F., Oparil, S., 1997. Estrogen restores endothelial cell function in an experimental model of vascular injury. *Circulation* 96, 1624–1630.
- Xu, Y., Arenas, I.A., Armstrong, S.J., Davidge, S.T., 2003. Estrogen modulation of left ventricular remodeling in the aged heart. *Cardiovasc. Res.* 57, 388–394.

ORIGINAL ARTICLE

Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities

Yumiko Mita,¹ Masahiro Akishita,¹ Katsuaki Tanaka,¹ Shizuru Yamada,¹
Ryuhei Nakai,² Eigo Tanaka,³ Tetsuro Nakamura⁴ and Kenji Toba¹

¹Department of Geriatric Medicine, Kyorin University School of Medicine, ³Mizukusaki-En and ⁴Research Institute of Aging Science, Tokyo, and ²Department of Neurology, Fukuoka University School of Medicine, Fukuoka, Japan

Background: The objectives of this study were to determine whether medications, particularly inappropriate prescribing, would be reduced after admission to long-term care facilities, and whether adverse drug withdrawal events (ADWEs) would occur in relation to discontinuation of medications.

Methods: The study consists of a retrospective survey using medical chart review in five health service facilities for the elderly in Japan. All the patients who were admitted to the facilities between January 2001 and December 2002 ($N = 627$) were participants in the study. Medications taken on admission, at 1 month and 3 months after admission, and events (significant worsening of the disease status, accidents, new symptoms and signs, and other acute events) during a 3-month period were recorded. Inappropriate prescribing was determined using Beers' criteria with some modification. ADWEs were determined using the Naranjo causality algorithm.

Results: On admission, the patients were taking 3.5 ± 2.5 (mean \pm SD) drugs. One month later, the number of prescribed drugs was decreased by 17% ($P < 0.01$ vs on admission), but did not show an additional reduction 3 months later. Inappropriate prescribing was found in 10% of the patients taking drugs on admission, but the number of inappropriately prescribed medications was reduced by 33% after 1 month. Of 105 events recorded, only five (2% of the patients with drug reduction) were considered ADWEs; three cases of confusion, a case of depression, and a case of hyperglycemia, following discontinuation of psychotropic drugs, antidepressants and a sulfonylurea, respectively.

Conclusion: Adverse drug withdrawal events were not frequent despite the significant reduction of medications after admission to long-term care facilities. This might be because the rate of reduction was relatively high for inappropriately prescribed medications.

Keywords: adverse drug reaction, long-term care, medical expense, medical injury, pharmacotherapy.

Introduction

Adverse drug reactions in elderly people increase with age,¹⁻³ with most being attributable to medication errors that are preventable.^{3,4} Age-dependent changes in pharmacokinetics and pharmacodynamics, polypharmacy and non-compliance related to patients' functional

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Correspondence, Masahiro Akishita, MD, PhD, Department of Geriatric Medicine, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Email: akishita-tky@umin.ac.jp

decline may play a role.^{1,3} In particular, polypharmacy resulting from multiple pathology in elderly people is a critical problem leading to adverse drug reactions.¹⁻³ To prevent polypharmacy, review of prescriptions is essential according to evidence-based medicine and criteria for inappropriate prescribing.^{5,6} In fact, inappropriate use of medication in elderly people has been reported to be as frequent as 16% to 25%.⁷⁻⁹

Conversely, discontinuation of medications to improve polypharmacy or inappropriate prescribing may induce adverse drug withdrawal events (ADWEs),¹⁰ although the net effect on adverse drug reactions can be favorable in elderly outpatients.¹¹ Fixed payment insurance systems restrict medication use, possibly leading to a reduction of inappropriate prescribing and/or an increase of ADWEs. In health service facilities for the elderly in Japan, where functional training and nursing/personal care are provided under long-term care insurance,¹² a fixed payment system including prescribing of medication is applied. Accordingly, it is hypothesized that prescribed drugs, particularly inappropriate prescribing, would be reduced after admission to the facilities, and that ADWEs would occur in relation to discontinuation of medications. To test this hypothesis, we performed a retrospective chart review of a total of 627 patients in five health service facilities for the elderly, and found that prescribed drugs can be reduced with few ADWEs in such a frail elderly population with chronic diseases.

Methods

Sample and data collection

The data were derived from five health service facilities for the elderly (Mahoroba-no-Sato, Nagano; Moeuno-Sato, Nagano; Himawari-En, Fukuoka; Millenium-Sakuradai, Tokyo; Mizukusaki-En, Tokyo) in Japan. Institutional medical charts were reviewed for all the patients admitted between January 2001 and December 2002. Diagnoses of each patient were not recorded because they were unclear from the institutional charts, but Alzheimer's disease, cerebrovascular disease and osteoporosis were the main causes of disability in each institution. The average basic activities of daily living, as measured by the Barthel index, were 70-80 points out of 100 points according to the institutions. Medications that the patients were taking on admission and prescribed drugs 1 month and 3 months after admission were recorded. Similarly, all the events (significant worsening of the disease status, accidents, new symptoms and signs, and other acute events) during a 3-month period were recorded. The institutions that managed the patients before admission were categorized as acute care hospitals, outpatient clinics (home), sanitarium-type wards, special nursing homes for the

elderly and health service facilities for the elderly. Patients with voluntary discharge within 3 months excluding cases of death or transfer to another hospital were excluded, and a total of 627 patients were analyzed. The director of each institution gave written approval to the participation in this study. The study protocol was approved by the committee on ethics and the institutional review board of Kyorin University School of Medicine.

Analysis

Inappropriately prescribed medications were determined using an updated version of the list developed by Beers with some modification.⁵ Basically, we followed the list by Sloane *et al.* in which several drugs were excluded from Beers' list in consultation with Dr Beers,^{5,9} reflecting changes in pharmacotherapy, but we included digoxin at more than 0.125 mg/day and oral iron at more than 325 mg/day in the list because these dosages were recorded in the medical chart. In this study, diagnosis-related inappropriate prescribing was excluded,³ as in the study by Sloane *et al.* because the institutional chart did not include all the diagnoses of the patients.⁹

All the events were reviewed by a consultant geriatrician, and ADWEs were determined using the Naranjo causality algorithm.¹³ Because detailed information, such as the effect of re-administration was lacking in most cases, a probability scale ≥ 1 (possible, probable or definite) was considered to indicate an ADWE.

The data in the text and the tables are expressed as means \pm SD unless otherwise specified. Changes in the number of prescribed drugs after admission were analyzed using paired *t*-test. Differences between the groups were analyzed using ANOVA followed by Newman-Keuls' test.

Results

Number of prescribed drugs

The patients were taking 3.5 ± 2.5 drugs when admitted to the facilities (Table 1). Forty-six patients (7.3%) were not taking any drug, while 50 patients (8.0%) were on eight or more drugs. Women were taking fewer drugs than men. This sex difference seemed independent of age, although a statistically significant difference was found only at 80-89 years of age when the patients were categorized by age groups (Table 1). Interestingly, patients of 80 years or older were taking fewer drugs than those younger than 70 years, in contrast to a previous finding that the number of prescribed drugs increased according to age.^{2,14,15}

As shown in Table 2, the mean number of prescribed drugs had decreased by 0.6 (17%) 1 month

Table 1 Number of drugs taken on admission according to sex and age

	All	Men	Women	<i>P</i> for sex difference
Total	3.5 ± 2.5 (627)	4.2 ± 2.8 (177)	3.3 ± 2.4 (450)	< 0.01
≤ 69 years	4.4 ± 3.1 (36)	4.6 ± 3.5 (19)	4.2 ± 2.6 (17)	0.70
70–79 years	4.0 ± 2.6 (131)	4.6 ± 3.0 (43)	3.7 ± 2.3 (88)	0.08
80–89 years	3.3 ± 2.3* (316)	4.0 ± 2.6 (81)	3.0 ± 2.2 (235)	0.02
≥ 90 years	3.5 ± 2.7* (144)	4.2 ± 2.4 (34)	3.2 ± 2.8 (110)	0.08

**P* < 0.05 versus ≤ 69 years by Newman-Keuls' test.

Data are expressed as mean ± SD. Number of subjects is indicated in parentheses.

Table 2 Changes in number of prescribed drugs after admission to health service facilities for the elderly

	No. of subjects	On admission	After 1 month	After 3 months
Total	627	3.5 ± 2.5	2.9 ± 2.2*	3.0 ± 2.1*
Type of institution before admission				
Acute care hospital	115	4.8 ± 3.3 [†]	4.2 ± 2.9 [†]	4.1 ± 2.7 [†]
Outpatient	200	3.6 ± 2.3	2.8 ± 1.8*	2.9 ± 2.0
Special nursing home	24	3.3 ± 2.1	2.5 ± 1.7*	2.6 ± 1.8*
Sanitarium-type ward	188	3.1 ± 2.3	2.6 ± 1.9*	2.6 ± 1.9*
Health service facility	100	2.6 ± 1.8	2.4 ± 1.6*	2.5 ± 1.7*
Facility				
A	83	4.9 ± 3.4	4.6 ± 3.0	4.6 ± 2.4
B	80	4.2 ± 2.8	3.9 ± 2.4*	4.0 ± 2.5
C	39	4.1 ± 2.7	2.4 ± 1.7*	2.2 ± 1.4*
D	172	3.2 ± 1.9	2.4 ± 1.5*	2.4 ± 1.5*
E	253	3.0 ± 2.2	2.6 ± 1.9*	2.5 ± 1.9
Event				
No	517	3.5 ± 2.5	2.8 ± 2.0*	2.8 ± 2.1*
Yes	104	3.6 ± 2.7	3.4 ± 2.5 ^{**†}	3.7 ± 2.2 ^{**†}

P* < 0.01 versus on admission by paired *t*-test; *P* < 0.01 versus after 1 month by paired *t*-test; [†]*P* < 0.01 versus other types of institution by Newman-Keuls' test; ****P* < 0.05; *0.01 versus Event (-) by Newman-Keuls' test.

Data are expressed as mean ± SD.

after admission (*P* < 0.01 versus on admission), but did not show an additional reduction 3 months after admission. A significant reduction was seen at 1 month irrespective of the type of institution that had managed the patients before admission, although the number of drugs on admission and the degree of reduction differed between the types of institutions. However, there was a large variation in the reduction of prescribed drugs between the facilities, presumably due to differences in the overall philosophy of the attending physicians and the disease and/or functional status of the patients. Patients with and without events during a 3-month period were analyzed separately (Table 2). They were taking a comparable number of medications on admission. The number of drugs in the patients with events was not significantly decreased at 1 month, and was rather increased at 3 months after admission because in many cases additional drugs were prescribed for treatment of events.

Discontinued drugs and inappropriate prescribing

Categorized by therapeutic class, discontinuation was frequent with neuropsychologic (121 cases), gastrointestinal (116 cases) and cardiovascular (94 cases) drugs, followed by metabolic/endocrine drugs (36 cases). Anti-ulcer drugs (44 cases) including H₂ blockers and prostaglandin analogs, antipsychotics (35 cases), antihypertensives (33 cases) including calcium channel blockers, β blockers and angiotensin converting enzyme inhibitors, hypnotics (31 cases), laxatives (31 cases) and non-steroidal anti-inflammatory drugs (22 cases) were frequently withdrawn.

On admission, inappropriate prescribing was seen in 58 patients (10.0% of 581 patients taking drugs). Ticlopidine, digoxin at more than 0.125 mg/day and oxybutynin were prescribed in five or more cases (Table 3). Inappropriately prescribed medications were reduced by 33% 1 month after admission, and did not change

Table 3 Number of inappropriately prescribed drugs on admission and 1 month after admission

Medication	On admission	After 1 month
Ticlopidine	36	25
Digoxin [†]	11	8
Oxybutynin	5	4
Amitriptyline	4	2
Benzodiazepines [‡]	3	1
Disopyramide	1	1
Indomethacin	1	1
Total	61	41

[†]More than 0.125 mg/day; [‡]Flurazepam, Chlordiazepoxide and Diazepam

thereafter (data not shown). The reduction was not restricted to specific drugs.

Events during admission

A total of 104 events were seen in 16.7% of the patients during a 3-month admission period. Frequent events (nine cases or more) were new occurrences or worsening of psychological disorders (14 cases); gastrointestinal symptoms (12 cases); respiratory problems, including aspiration, pneumonia and respiratory failure (10 cases); pyrexia and infection other than pneumonia (10 cases); and falls and fractures (nine cases).

Five cases of ADWEs were found in 2.2% of 230 patients with drug reduction. These included three cases of confusion following discontinuation of psychotropic drugs, a case of depression following discontinuation of antidepressants and a case of hyperglycemia following discontinuation of a sulfonylurea.

Subgroups analyses were performed to examine the bias effect on events. The rates of events by type of institutions before admission were 24.5% in the subjects from acute care hospitals, 18.1% in those from outpatient clinics (not significant compared to other groups) and 13.1% in those from other types of institutions ($P < 0.05$ versus the subjects from acute care hospitals). Specific types of events were not related to the higher rate of events in the subjects from acute care hospitals, suggesting that unstable conditions of these patients may play a role. Of five cases with ADWEs, three were found in the subjects from outpatient clinics, one from special nursing homes and one from sanitarium-type wards. Thus, it is likely that possible non-compliance in outpatients or types of institutions before admission did not influence the principal results concerning ADWEs.

The subjects in facilities A and B (Table 2), in which significant drug reduction was not observed, showed a higher rate of events than those in other facilities (28.1% versus 12.9%, $p < 0.001$). This result indicates that adverse drug reactions associated with polyphar-

macy would have been included in these events, or additional drugs would have been prescribed for treatment of events, although no specific type of events was noted regarding the difference between the facilities. No ADWEs were found in the subjects in facilities A and B, presumably relating to the continuation of medications.

Discussion

The present study showed that the number of prescribed drugs was significantly decreased within 1 month after admission to health service facilities for the elderly. Discontinuation was not limited to inappropriate prescribing, but a larger proportion of inappropriately prescribed medications were discontinued compared to the total reduction of prescribed drugs (33% versus 17%). ADWEs were not frequent, being found in only 2.2% of the patients with drug reduction, while unrelated events occurred in 16.7% of the total patients.

Reflecting on the high incidence of polypharmacy and adverse drug reactions in elderly patients,^{1-3,14} the principal finding of the present study that prescribed drugs can be reduced safely in frail elderly patients provides important information on pharmacotherapy. Every physician may make an effort to prescribe the minimum number of drugs, but a patient's long history of illness results in the accumulation of prescribed drugs together with the uncertain efficacy of the drugs. Consequently, the necessity of each medication should be reviewed regularly according to evidence-based medicine and criteria for inappropriate prescribing.^{5,6} There is a great opportunity to reconsider prescriptions when attending physicians and/or the insurance system change, as was the case with the present study.

The number of prescribed drugs on admission in this study was smaller than that found in the geriatric ward of our university hospital and that found in residential care/assisted living facilities in the USA.^{2,9} This may be because nearly half of the subjects were admitted from long-term care hospitals or facilities, and thus, prescribed drugs had already been restricted. In fact, patients from acute care hospitals were taking more drugs than those from other types of institution. It is interesting that an older age was associated with a smaller number of prescribed drugs, and this did not change when the data were analyzed according to the type of institution from which the patients had come (data not shown). This finding is inconsistent with previous observations in hospitalized or community-dwelling patients,^{2,14,15} but is reasonable to prevent non-compliance and adverse drug reactions. At the same time, however, the age-related decrease in medications may involve possible discrimination towards very old people. The smaller number of prescribed drugs in women and discontinuation of medications after

admission in this study are inconsistent with previous reports,^{16,17} and may imply age and sex discrimination, although discontinuation seemed successful in this study. Thus, the discrimination issue should also be taken into consideration concerning pharmacotherapy in older people.

In the present study, ADWEs were fewer than the previously reported study in which 26% of cases of discontinuation led to ADWEs in elderly outpatients during a 4-month period.¹⁰ One of the reasons that ADWEs were rare in the present study might be that the rate of reduction was relatively high for inappropriately prescribed medications, although most of the attending physicians did not know the criteria for inappropriate prescribing such as Beers' list.⁵ Another reason is that consultant physicians or geriatricians made decisions on prescriptions, based on the disease and functional status of each patient. In fact, most of discontinued drugs were not on the list of inappropriate prescribing, implying that unnecessary drugs had been prescribed before admission to long-term care facilities. In addition, it is possible that we missed ADWEs that progressed very slowly and manifested after the follow-up period of 3 months. We also failed to address the effect of prophylactic medications such as antiplatelet and lipid-lowering agents.

It should be kept in mind that the present results were obtained in a frail elderly population admitted to long-term care facilities where most of the subjects were in a stable state with chronic illness.¹² However, as a model to investigate the effect of drug reduction in elderly people, the present findings will add new insight into pharmacotherapy in the elderly, and should be confirmed in different settings such as hospitals and outpatient clinics. Obviously, medications for acute illness should neither be decreased, nor should physicians hesitate to initiate them even in very old patients, and in fact, prescribed drugs were increased in the patients with events during admission in this study. To safely apply the findings of the present study to clinical practice, knowledge of the criteria for inappropriate prescribing should be widely distributed, and blanket discontinuation of drugs must be avoided. In the present study, we used the Beers' criteria to determine inappropriately prescribed medications because corresponding criteria do not exist in Japan.⁵ Consequently, we failed to check many inappropriate drugs that are used in Japan but are not on the Beers' list or sold in the USA. Future investigation using the Japanese criteria for inappropriate prescribing, which the Japan Geriatrics Society is going to establish, will add more information. In Japan, the fixed payment insurance system has begun to cover elderly patients, with the expansion of the elderly population and medical expenses. Therefore, it is essential to establish an effective and safe way to refine the use of medication in

elderly people in terms of prevention of adverse drug reactions and ageism.

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References

- Hanlon JT, Shimp LA, Semla TP. Recent advances in geriatrics: drug-related problems in the elderly. *Ann Pharmacother* 2000; **34**: 360-365.
- Akishita M, Toba K, Nagano K, Ouchi Y. Adverse drug reactions in older people with dementia. *J Am Geriatr Soc* 2002; **50**: 400-401.
- Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; **160**: 2717-2728.
- Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983 and 1993. *Lancet* 1998; **351**: 643-644.
- Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531-1536.
- Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992; **45**: 1045-1051.
- Spore DL, Mor V, Larrat P, Hawes C, Hiris J. Inappropriate drug prescriptions for elderly residents of board and care facilities. *Am J Public Health* 1997; **87**: 404-409.
- Hanlon JT, Schmader KE, Boult C et al. Use of inappropriate prescription drugs by older people. *J Am Geriatr Soc* 2002; **50**: 26-34.
- Sloane PD, Zimmerman S, Brown LC, Ives TJ, Walsh JF. Inappropriate medication prescribing in residential care/assisted living facilities. *J Am Geriatr Soc* 2002; **50**: 1001-1011.
- Graves T, Hanlon JT, Schmader KE et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med* 1997; **157**: 2205-2210.
- Hanlon JT, Weinberger M, Samsa GP et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med* 1996; **100**: 428-437.
- Hirakawa Y, Masuda Y, Uemura K et al. Current admission policies of long-term care facilities in Japan. *Geriatrics Gerontol Int* 2003; **3**: 73-78.
- Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245.
- Stewart RB, Cooper JW. Polypharmacy in the aged. Practical solutions. *Drugs Aging* 1994; **4**: 449-461.
- Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivela SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol* 2002; **55**: 809-817.
- Martin I, Hall J, Gardner T. Prescribing for patients aged 65 years and over in New Zealand general practice. *N Z Med J* 2002; **115**: U221.
- Koopmans RT, van der Borgh JP, Bor JH, Hekster YA. Increase in drug use after admission to Dutch nursing homes. *Pharm World Sci* 2003; **25**: 30-34.