Table 2 Indications for tube feeding and interventions for dysphagia before introducing tube feeding according to place of employment and clinical experiences

Questions	Characteristics of geriatricians Place of employment Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	P-value	Clinical experience <30 years $n = 317$	≧30 years $n = 238$	P-value	Total $n = 555$
Is the following disorder an indication for TF?									
Head injury or facial trauma	313 (86.9)	144 (86.7)	8 (40.0)	7 (77.8)	ND	208 (88.3)	192 (80.7)	0.012	472 (85.0)
Oropharyngeal malignancy	286 (79.4)	143 (86.1)	13 (65.0)	7 (77.8)	ND	258 (81.4)	191 (80.3)	0.736	449 (80.9)
Neurological disorder	328 (91.1)	155 (93.4)	15 (75.0)	7 (77.8)	ND	295 (93.1)	210 (88.2)	0.049	505 (91.0)
Stroke	334 (92.8)	147 (88.6)	18 (90.0)	8 (88.9)	ND	290 (91.5)	217 (91.2)	0.899	507 (91.4)
Dementia	177 (49.2)	66 (39.8)	13 (65.0)	4 (44.4)	ND	1156 (49.2)	104 (43.7)	0.198	260 (46.8)
Aspiration-prone frail elderly without comorbidity	238 (66.1)	108 (65.1)	15 (75.0)	5 (55.6)	ND	216 (68.1)	150 (63.0)	0.208	366 (65.9)
Malnutrition in frail elderly without comorbidity	115 (31.9)	58 (34.9)	9 (45.0)	5 (55.6)	ND	115 (36.3)	72 (30.3)	0.137	187 (33.7)
How long does a patient need to survive after PEG placement?‡									
2 weeks	3 (0.8)	2 (1.2)	0 (0.0)	0 (0.0)	ND	3 (0.9)	2 (0.8)	ND	5 (0.9)
4 weeks	19 (5.3)	16 (9.6)	1 (5.0)	2 (22.2)	–	18 (5.7)	20 (8.4)	–	38 (6.8)
6 weeks	4 (1.1)	2 (1.2)	1 (5.0)	1 (11.1)	–	7 (2.2)	1 (0.4)	–	8 (1.4)
8 weeks	39 (10.8)	21 (12.7)	3 (15.0)	0 (0.0)	–	37 (11.7)	26 (10.9)	–	63 (11.4)
12 weeks	295 (81.9)	125 (75.3)	15 (75.0)	6 (66.7)	–	252 (79.5)	189 (79.4)	–	441 (79.5)
Interventions for swallowing disorder before introducing TF									
No. Interventions; mean ± standard deviation (total 15 items)	6.44 ± 3.12*	5.83 ± 2.93	6.70 ± 2.00	3.67 ± 3.32*	0.010§	6.49 ± 3.20	5.86 ± 2.82	0.015	6.22 ± 3.06
No. interventions, ≧6 items¶ (total 15 items)	211 (58.6)	84 (50.6)	14 (70.0)	2 (22.2)	ND	188 (59.3)	123 (51.7)	0.073	311 (56.0)
Consultation									
To otolaryngologist	131 (36.4)	60 (36.1)	3 (15.0)	4 (44.4)	ND	123 (38.8)	75 (31.5)	0.076	198 (35.7)
To speech therapist	166 (46.1)	31 (16.7)	7 (35.0)	1 (11.1)	ND	131 (41.3)	74 (31.1)	0.013	205 (36.9)
To certified nurse of dysphagia nursing	77 (21.4)	25 (15.1)	4 (20.0)	2 (22.2)	ND	67 (21.1)	41 (17.2)	0.250	108 (19.5)
Test									
Repetitive saliva swallowing test	111 (30.8)	63 (38.0)	4 (20.0)	2 (22.2)	ND	109 (34.4)	71 (29.8)	0.257	180 (32.4)
Water swallowing test	243 (67.5)	104 (62.7)	13 (65.0)	5 (55.6)	ND	210 (66.2)	155 (65.1)	0.783	365 (65.8)
Video endoscopy	55 (15.3)	26 (15.7)	1 (5.0)	0 (0.0)	ND	50 (15.8)	32 (13.4)	0.444	82 (14.8)
Video fluorography	163 (45.3)	47 (28.3)	4 (20.0)	2 (22.2)	ND	140 (64.8)	76 (31.9)	0.003	216 (61.1)
Practice and education									
Oral ice-massage	102 (28.3)	23 (13.9)	5 (25.0)	0 (0.0)	ND	86 (27.1)	44 (18.5)	0.017	130 (23.4)
Swallowing exercise	72 (20.0)	40 (24.1)	5 (25.0)	0 (0.0)	ND	70 (22.1)	47 (19.7)	0.505	117 (21.1)
Vocalization exercise	50 (13.9)	20 (12.0)	1 (5.0)	0 (0.0)	ND	44 (13.9)	27 (11.3)	0.376	71 (12.8)
Using semi-solid and liquid foods	267 (74.2)	120 (72.3)	18 (90.0)	3 (33.3)	ND	236 (74.4)	172 (72.3)	0.565	408 (73.5)
Thickening agent	308 (85.6)	131 (78.9)	20 (100.0)	3 (33.3)	ND	267 (84.2)	195 (81.9)	0.474	462 (83.2)
Positioning	235 (65.3)	106 (63.9)	17 (85.0)	4 (44.4)	ND	215 (67.8)	147 (61.8)	0.138	362 (65.2)
Appropriate approach for swallowing	161 (44.7)	80 (48.2)	12 (60.0)	2 (22.2)	ND	153 (48.3)	102 (42.9)	0.206	255 (45.9)
Ways of coping with aspiration	161 (44.7)	85 (51.2)	17 (85.0)	4 (44.4)	ND	142 (44.8)	125 (52.5)	0.071	267 (48.1)

Number (%), P-values were tested by χ^2-test and Student's t-test, †Other included part-time doctors, retired doctors, researchers and so on. ‡Single answer was allowed for five items, and the other questions were allowed to select more than one. §P-values were tested by ANOVA, *$P < 0.05$ by Bonferroni. ¶Number of intervention items were divided into two groups, which used median value (≧6 *vs* <6). ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

feeding by PEG.[7,8,10,12] In addition, "Guideline of parenteral and EN for elderly in Europe" does not recommend enteral nutrition to persons with severe dementia as a result of more risks than benefits for persons with severe dementia, and occasionally in early and moderate dementia to ensure energy and nutrient supply and to prevent undernutrition.[17,18] In the present study, we found that approximately 45% of the geriatricians considered that dementia patients with loss of appetite or apraxia for eating should be on tube feeding and that 65% of the geriatricians considered that aspiration-prone frail elderly without comorbidities should also be on tube feeding, which is a relatively high percentage. In a previous study, approximately 60% of physicians in the USA answered that aspiration pneumonia was the indication for PEG placement, and was the most common medical indication.[19] The present finding are consistent with other results; therefore the medical situation in Japan might be quite similar to that in the USA. Indeed, PEG placement to the elderly with repeating aspiration pneumonia or not eating voluntarily with cerebrovascular disease or dementia is indicated in "Guideline of PEG in Japan."[16] In the present study, the questions did not specify the stage of disorders or the level of conditions; therefore our results should be interpreted with caution. However, it is certain that there is no consensus among Japanese geriatricians about tube feeding for the elderly with advanced dementia and there is an urgent need to develop guidelines to decide the risk/benefit ratio in the individual patient to optimize the timing and route of nutritional support. Thus, the indication for tube feeding in the elderly should be widely discussed in the future and hence a guideline should be established to describe the indication of tube feeding in more detail.

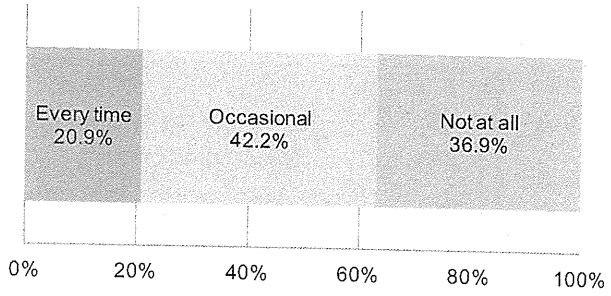

Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

"Guideline of parenteral and EN for elderly in Europe" indicates PEG placement if EN is anticipated for longer than 4 weeks.[17,18] In contrast, the present study showed that approximately 80% of the geriatricians consider that survival more than 12 weeks should be expected for PEG placement. PEG is better than NGT for swallowing rehabilitation, and PEG placement

Table 3 Conference members for decision making of tube feeding according to place of employment

	Place of employment of geriatricians					Total
	Hospital $n = 249$	Clinic $n = 80$	Long-term care $n = 17$	Other† $n = 3$	*P*-value	$n = 350$
No. conference members; mean ± standard deviation (total 12 occupations)	4.4 ± 2.0	4.2 ± 1.8	4.3 ± 1.5	4.8 ± 4.2	0.864	4.31 ± 1.9
Conference members						
Attending physician	238 (95.2)	75 (92.6)	17 (100)	3 (100)	–	334 (95.4)
Primary nurse	224 (89.6)	54 (66.7)	15 (88)	3 (100)	–	297 (94.9)
Otolaryngologist	27 (10.8)	10 (12.3)	0 (0)	0 (0.0)	–	37 (10.6)
Certified nurse of dysphagia nursing	42 (16.8)	18 (22.2)	3 (18)	0 (0.0)	–	63 (18.0)
Physical therapist	55 (22.0)	12 (14.8)	4 (24)	1 (33.3)	–	72 (20.6)
Occupational therapist	37 (14.8)	8 (9.9)	4 (24)	1 (33.3)	–	50 (14.3)
Speech therapist	118 (47.2)	23 (28.4)	5 (29)	1 (33.3)	–	147 (42.0)
Dietician	126 (50.4)	37 (45.7)	9 (53)	2 (66.7)	–	174 (49.7)
Pharmacist	37 (14.8)	12 (14.8)	1 (5.9)	1 (33.3)	–	51 (14.6)
Discharge planning coordinator‡	26 (10.4)	14 (17.3)	2 (12)	1 (33.3)	–	43 (12.3)
Medical social worker	89 (35.6)	24 (29.6)	4 (24)	2 (66.7)	–	119 (34.0)
Care manager	46 (18.4)	39 (48.1)	5 (29)	1 (33.3)	–	91 (26.0)

Number (%), *P*-values were tested by ANOVA, $^*P < 0.05$ by Bonferroni. Of the 555 geriatricians, 350 (63.1%) carried out a conference at least once. Respectively, hospital: 249 (69.2%), clinic: 80 (48.2%), long-term care: 17 (85.0%), other: 3 (33.3%). Multiple answers were allowed. †Other included part-time doctors, retired doctors, researchers and so on. ‡They are a registered nurse and work for discharge planning and coordination in the hospital.

Table 4 Multivariate-adjusted odds ratios and 95% confidence intervals for frequency and the conference members according to the indication for tube feeding and interventions for dysphagia before using tube feeding

	Conference				
	Non	Occasional		Every time	
		Participating occupation		Participating occupation	
		Few	Multidisciplinary	Few	Multidisciplinary
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Is the following disorder an indication for TF?					
Head injury or facial trauma	Ref	1.02 (0.55–1.89)	1.15 (0.52–2.57)	0.80 (0.36–1.78)	1.52 (0.62–3.77)
Oropharyngeal malignancy	Ref	0.96 (0.56–1.66)	0.78 (0.41–1.52)	1.05 (0.48–2.31)	1.02 (0.48–2.16)
Neurological disorder	Ref	0.72 (0.34–1.52)	0.56 (0.23–1.34)	1.69 (0.46–6.16)	1.17 (0.39–3.53)
Stroke	Ref	1.41 (0.68–2.90)	1.84 (0.66–5.13)	2.35 (0.68–8.15)	4.03 (0.90–18.05)
Dementia	Ref	0.83 (0.54–1.28)	0.82 (0.48–1.42)	1.86 (1.00–3.44)	1.01 (0.56–1.83)
Aspiration-prone frail elderly without comorbidity	Ref	0.99 (0.63–1.55)	1.23 (0.69–2.19)	1.31 (0.68–2.52)	0.80 (0.44–1.46)
Malnutrition in frail elderly without comorbidity	Ref	0.77 (0.49–1.22)	0.98 (0.56–1.74)	1.30 (0.70–2.42)	1.18 (0.64–2.18)
How long does a patient need to survive after PEG placement? ≧12 weeks†	Ref	0.85 (0.50–1.43)	0.89 (0.46–1.74)	0.80 (0.39–1.63)	1.44 (0.64–3.21)
Intervention for swallowing disorder before using TF					
No. intervention items, ≧ 6 items‡	Ref	2.07 (1.33–3.20)	3.24 (1.81–5.78)	2.60 (1.39–4.85)	8.71 (3.99–19.00)
Consultation					
To otolaryngologist	Ref	1.13 (0.72–1.77)	1.36 (0.78–2.38)	0.94 (0.49–1.80)	1.48 (0.80–2.72)
To speech therapist	Ref	1.51 (0.93–2.46)	4.57 (2.52–8.29)	2.47 (1.28–4.76)	3.82 (2.01–7.27)
To certified nurse of dysphagia nursing	Ref	1.18 (0.65–2.14)	2.16 (1.11–4.23)	1.65 (0.76–3.61)	4.75 (2.43–9.32)
Test					
Repetitive saliva swallowing test	Ref	1.62 (0.98–2.66)	3.89 (2.16–6.99)	3.91 (2.05–7.44)	4.48 (2.37–8.46)
Water swallowing test	Ref	2.08 (1.32–3.28)	1.63 (0.93–2.87)	1.82 (0.96–3.44)	2.95 (1.49–5.88)
Video endoscopy	Ref	1.53 (0.83–2.82)	1.30 (0.59–2.86)	0.97 (0.37–2.53)	2.89 (1.37–6.09)
Video fluorography	Ref	1.62 (1.03–2.56)	2.08 (1.19–3.66)	3.07 (1.64–5.76)	2.28 (1.23–4.22)
Practice and education					
Oral ice-massage	Ref	1.19 (0.67–2.10)	2.19 (1.16–4.14)	2.34 (1.14–4.79)	3.59 (1.82–7.06)
Swallowing exercise	Ref	1.81 (0.97–3.39)	3.47 (1.74–6.91)	4.86 (2.34–10.09)	6.63 (3.27–13.45)
Vocalization exercise	Ref	1.55 (0.71–3.41)	2.96 (1.28–6.83)	2.70 (1.04–7.00)	6.84 (3.02–15.50)
Using semi-solid and liquid foods	Ref	1.83 (1.13–2.96)	2.12 (1.11–4.06)	1.71 (0.86–3.38)	5.96 (2.24–15.84)
Thickening agent	Ref	1.26 (0.73–2.21)	1.93 (0.85–4.39)	1.18 (0.54–2.59)	4.68 (1.36–16.12)
Positioning	Ref	1.46 (0.94–2.26)	2.36 (1.29–4.31)	1.75 (0.93–3.30)	7.22 (2.94–17.71)
Appropriate approach for swallowing	Ref	2.48 (1.59–3.88)	2.82 (1.62–4.92)	2.13 (1.15–3.95)	5.60 (2.94–10.65)
Ways to coping when the aspiration	Ref	1.48 (0.95–2.29)	2.86 (1.63–5.01)	1.24 (0.67–2.29)	5.31 (2.69–10.48)

Dependent variables: the indication for tube feeding and interventions for dysphagia before introducing tube feeding. Independent variables: frequency and the conference members (ref, non conference; 1, occasional and less than five different health-care professionals; 2, occasional and ≧5 different health care professionals; 3, every time and less than five different health-care professionals; 4, every time and ≧5 different health-care professional. Adjusted for sex, place of employment and clinical experience. †The period expected to survive after PEG was divided into two groups. (1: ≧12 weeks, 0: <12 weeks). ‡Number of intervention items were divided into two groups, which was used median value into 15 items. (1: ≧6 items, 0: <6 items). CI, confidence interval; OR, odds ratio; TF, Tube Feeding.

in patients with stroke and oropharynegeal malignancy was associated with better prognosis; therefore PEG placement is recommended for these disorders by the European guideline.[20] We did not investigate how long PEG is placed in each condition. Thus, knowledge of geriatricians for tube feeding or PEG placement was not sufficiently explored in the present study; however, a period of PEG placement should be considered in each condition.

In Japan, requests for PEG to facilitate care are prevalent, because the staff in nursing homes tend to prefer PEG to time-consuming oral feeding. A multicenter study in the USA showed that feeding tube insertion is independently associated with both clinical characteristics of residents and fiscal, organizational and demographic features of nursing homes.[4] Therefore, these situations might have affected the decision making of geriatricians for tube feeding. Unfortunately, we did not include the question whether or not the request from nursing homes might have affected the decision making for tube feeding in dementia patients. Therefore, we should ask this question next time.

Regarding interventions for swallowing disorder, the mean number of interventions for swallowing disorder before introducing tube feeding was six items, which are not so many. Among the 15 items of interventions before introducing tube feeding, over 70% of the geriatricians answered that "Thickening agent" and "Using semi-solid and liquid foods" were afforded to patients with swallowing disorder. In contrast, consultation with other specialists was not frequently carried out, and care to improve swallowing dysfunction, such as "oral ice-massage," "swallowing exercise" and "vocalization exercise" was not usually carried out either. Therefore, from these data, we think that more interventions would be necessary to care for patients with dysphagia by consulting specialists and multidisciplinary approach.

It is interesting to note the relationship between multidisciplinary conference and knowledge and practice for tube feeding for the elderly. In the present study, we showed that those who have a multidisciplinary team conference for a patient indicated for tube feeding tended to carry out more "interventions for dysphagia before tube feeding" compared with the reference group after multivariate adjustment. Furthermore, the data showed that geriatricians who organize a conference with different health-care professionals carried out more interventions for dysphagia before tube feeding, irrespective of the frequencies of conference. The present study also showed that although there were no differences in the number of conference members and interventions between the geriatricians working in an acute hospital and those in a clinic before introducing tube feeding, the percentage of geriatricians who organized a multidisciplinary conference before introducing tube feeding was higher in the hospital than in the clinic. Therefore, the characteristics of facilities, not doctors themselves, might have affected this outcome. A previous study reported that multidisciplinary CGA is effective for the care of frail older persons admitted to the hospital, because evaluation and management by a multidisciplinary team during hospitalization documented a lower rate of institutionalization after 1 year.[14] Furthermore, decision making for treatment strategy should be discussed in a multidisciplinary team. The multidisciplinary conference would provide a better answer for each elderly patient who requires tube feeding, because they tend to have a complicated background.

Several potential limitations should be considered when interpreting these results. First, a cross-sectional study does not prove any causal relationship. Second, the practice rate of tube feeding in geriatricians was not clearly determined, because the present study was carried out by self-administered questionnaires. Third, the subjects were limited to geriatricians certified by the Japan Geriatrics Society, and also the response rate was not so high. Therefore, selection bias might have occurred. Finally, we did not investigate the number of beds in their place of employment; therefore these results were not completely adjusted by hospital size.

In conclusion, the present data showed that more than half of the board-certified geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. Furthermore, regardless of their clinical experience, approximately 40% of the Japanese geriatricians consider that demented elderly with loss of appetite or apraxia for eating should be on tube feeding. At this moment, there is no consensus among Japanese geriatricians about tube feeding for advanced demented people, and hence the guideline should be established for tube feeding in the elderly. Furthermore, a multidisciplinary team approach is expected to find a better answer for each elderly patient with eating difficulty.

Acknowledgments

We thank all geriatricians in Japan for their kind help and advice during the present research. We also thank Priscila Yukari Sewo Sampaio for critical reading of our manuscript. This study was supported by a Grant-in-Aid (H22-Tyojyu-009) from the Ministry of Health, Labour and Welfare, Japan.

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Hypertension Research (2012), 1–7

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REVIEW SERIES

Hormonal effects on blood vessels

Masahiro Akishita[1] and Jing Yu[2]

The incidence of cardiovascular disease (CVD) is lower in younger women than in men of the same age, but it increases after menopause, implicating the atheroprotective action of endogenous estrogen. Although observational studies have suggested the efficacy of estrogen therapy in postmenopausal women, placebo-controlled, randomized trials, such as the Women's Health Initiative, have not confirmed effects of estrogen therapy on CVD. Conversely, basic, experimental research has progressed and provided mechanistic insight into estrogen's action on blood vessels. By contrast, the vascular effects of androgens remain poorly understood and have been controversial for a long time. In recent years, an increasing body of evidence has suggested that androgens may exert protective effects against the development of atherosclerosis, at least in elderly men. Epidemiological studies have shown that the incidence of and mortality due to CVD were increased in elderly men with low testosterone levels, although the efficacy of androgen therapy remains unknown. Furthermore, recent experimental studies have demonstrated the direct action of androgens on the vasculature. In this review, we illustrate the effects of sex steroids on the cardiovascular system, focusing on the action of testosterone on the blood vessels.
Hypertension Research advance online publication, 2 February 2012; doi:10.1038/hr.2012.4

Keywords: cardiovascular disease; endothelium; estrogen; testosterone; vascular smooth muscle

INTRODUCTION

Since the 1940s, it has been recognized that sex steroids have important roles in the cardiovascular system.[1,2] A number of epidemiological studies have shown that sex differences are apparent in the incidence of atherosclerotic disease. The incidence of cardiovascular diseases (CVDs), such as hypertension and coronary artery disease, is lower in younger women than in men of the same age.[3–5] However, it rises after menopause and, with age, catches up to that among men. These phenomena have been explained by the atheroprotective action of endogenous estrogen and its deprivation in postmenopausal women. In the past 20–30 years, many studies have suggested the efficacy of hormone replacement therapy (HRT) in postmenopausal women for the prevention of CVD and the putative vasoprotective effects of estrogen. However, reports from the Heart and Estrogen-Progestin Replacement Study (HERS)[6] and the Women's Health Initiative (WHI)[7] denied the efficacy of estrogen therapy in CVD.

By contrast, the actions of androgens on the cardiovascular system remain unclear. In the process of atherosclerosis, androgens may exert complex effects on vessel walls. Both beneficial and detrimental effects have been reported. For many years, it was widely believed that androgens have unfavorable roles in the development of atherosclerosis. Recently, however, the link between androgen deficiency and atherosclerosis has been demonstrated in a number of studies.[8–10] Various epidemiological and experimental studies have also demonstrated that androgens exert beneficial influences on CVD via the direct and indirect action of androgens on the blood vessels.

As the effects of estrogen on the cardiovascular system have been extensively studied and reviewed,[11–14] we allocated a small portion of our research to estrogen, highlighting recent developments. A larger part of this review focuses on androgens, particularly testosterone, to discuss the biological role of testosterone in vascular physiology and pathology in aging men.

ACTION OF ESTROGEN ON THE CARDIOVASCULAR SYSTEM

Effects of estrogen on cardiovascular risk factors

A number of studies have reported that estrogen therapy in postmenopausal women decreases the serum levels of both total and low-density lipoprotein cholesterol while raising high-density cholesterol and triglycerides, primarily by influencing the expression of hepatic apoprotein genes.[11,15] Also, estrogen inhibits the lipid peroxidation of low-density lipoprotein *in vitro* and *in vivo*.[16,17] Furthermore, estrogen can modulate glucose metabolism and prevent other risk factors for CVD, such as obesity (Table 1).[18,19]

Direct vascular action of estrogen

Two estrogen receptor (ER) subtypes, ERα and ERβ, have been identified and are expressed in the vasculature, and experimental studies have demonstrated the vasodilator effects of estrogen/ER through their action on the endothelium, smooth muscle and extracellular matrix. Estrogen enhances endothelium-dependent vasorelaxation via increased release of nitric oxide (NO),[20–22] endothelium-derived hyperpolarizing factor[23] and PGI_2[24,25] and decreased production of endothelin-1 (Table 1).[26] Several studies have demon-

[1]Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan and [2]Department of Integrated Traditional Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
Correspondence: Dr M Akishita, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail: akishita-tky@umin.ac.jp
Received 5 September 2011; revised 17 November 2011; accepted 12 December 2011

Table 1 Anti-atherosclerotic effects of estrogen

Risk factors	*Vascular action*
Lipid metabolism	Endothelium-dependent vasorelaxation
HDL cholesterol↑	Nitric oxide↑
LDL cholesterol↓	Endothelin-1↓
Lp (a)↓	EDHF↑
Anti-oxidant	PGI_2↑
Glucose metabolism	Inhibition of EC apoptosis
Anti-obese	Endothelium-independent vasorelaxation
	Calcium antagonistic
	Inhibition of VSMC migration/proliferation

Abbreviations: EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VSMC, vascular smooth muscle cell.

strated that estrogen inhibits calcium influx[27,28] and stimulates calcium efflux[29] in vascular smooth muscle cells (VSMCs), leading to endothelium-independent vasodilation. Moreover, estrogen inhibits neointima formation in response to balloon injury[30,31] and perivascular cuff placement.[32] Endothelial regeneration,[33] inhibition of endothelial apoptosis[34] and inhibition of VSMC migration and proliferation[32] may account for the inhibitory effects of estrogen on neointima formation. Analyses of knockout mice for ERα and ERβ have provided more information regarding the molecular mechanism of estrogen's action on the blood vessels.[5] Recent progress in nuclear receptor research has also clarified the non-genomic action of estrogen on the vasculature,[14] such as the direct interaction of ERα with the regulatory subunit of phosphatidylinositol-3-OH kinase.[35]

Role of the novel ER G protein coupled receptor 30 (GPR30) in the cardiovascular system

In addition to the two classical ER subtypes, ERα and ERβ, a third membrane-bound and G-protein-coupled ER, GPR30, has been identified in human vascular endothelial cells (ECs) and smooth muscle cells.[36–38] Haas *et al.*[37] reported that G-1, a selective stimulator of GPR30, acutely blocked vasoconstrictor-induced changes in intracellular calcium concentrations and vascular tone, resulting in lowering of blood pressure in normotensive rats. Similar vasodilator effects of GPR30 have been confirmed in other studies.[39–41] It has also been reported that stimulation of GPR30 blocks VSMC proliferation.[37,42]

The vasodilator action of G-1 may be mediated by NO-independent[40] and NO-dependent[37,39,40] pathways; the latter involves GPR30-induced endothelial NO synthase (eNOS) phosphorylation.[43] Also, G-1 decreases nicotinamide adenine dinucleotide phosphate-stimulated superoxide production by the carotid and intracranial arteries, indicating the scavenging effects of GPR30 on superoxide anions.[39] In the heart, G-1 reduces ischemia/reperfusion injury and preserves cardiac function through the phosphatidylinositol 3-kinase/Akt and extracellular signal-regulated kinase pathways and by eNOS phosphorylation.[44,45] Treatment with G-1 for 2 weeks reduced the expression of angiotensin II type 1 receptor and angiotensin-converting enzyme.[40] The non-selective ER antagonist ICI 182780 and selective ER modulators, such as tamoxifen and raloxifene, have been shown to act as GPR30 ligands.[46] Moreover, both GPR30 and ER are required for estrogen action in some situations, whereas GPR30 can act alone in the absence of ER,[46,47] suggesting a complex network between GPR30 and ER.

HRT and CVD

Observational studies have suggested that HRT decreases the risk of CVD in postmenopausal women.[48,49] However, large-scale, placebo-controlled, randomized trials, such as the HERS[6] and the WHI,[7] did not confirm the findings of the observational studies. In the WHI, HRT with conjugated equine estrogen plus medroxyprogesterone acetate increased the incidence of CVD instead, particularly in women older than 60 years of age, although women who started HRT soon after menopause tended to have a decreased risk for coronary heart disease.[50]

Additional data from other studies have supported the concept that the vasoprotective effects of estrogen are evident only when hormone therapy is initiated soon after the onset of menopause and before the development of atherosclerosis. In a meta-analysis of hormone therapy, CVD mortality was lower in younger women on hormone therapy (mean age of 55 years old) than in age-matched controls.[51] Women aged 50–59 years who were enrolled in the conjugated equine estrogen trial of the WHI had significantly lower scores for coronary artery calcification 8.7 years after randomization than with placebo.[52]

Two ongoing clinical trials, the Kronos Early Estrogen Prevention Study[53] and the Early Versus Late Intervention Trial with Estradiol Study (available at http://clinicaltrials.gov/ct2/show/NCT00114517; accessed 16 November 2011), were designed to examine the timing, dosage, route and limited duration of administration on patients' cardiovascular outcomes and to prove the benefits of HRT in atherosclerosis when HRT is initiated soon after menopause. In the near future, these trials will provide additional insight into HRT and cardiovascular health in younger postmenopausal women.

ASSOCIATION OF LOW TESTOSTERONE LEVELS WITH CVD

Plasma testosterone levels decrease with aging, and >20% of healthy men older than 60 years of age have testosterone levels below the standard range in young men aged 20–30 years.[54,55] Lower testosterone levels are associated with cognitive dysfunction, muscle weakness, anemia, osteoporosis, mood disturbances and impaired general and sexual health in aging men.[56,57] Recently, many studies have demonstrated the relationship of testosterone with CVD, indicating a consistent inverse relationship between endogenous testosterone and adverse cardiovascular events.

A case–control study among 117 Indian men aged 30–60 years with old myocardial infarction showed that testosterone concentrations were significantly lower in the patients with myocardial infarction than in the control subjects.[58] Similar results were reported in men with acute myocardial infarction.[59] Cross-sectional results from the Massachusetts Male Aging Study (1709 men aged 40–70 years) showed that serum total and free testosterone levels bear an inverse relationship with CVD, independent of cardiovascular risk factors.[60] Recently, epidemiological studies have found that low testosterone levels are a predictor of all-cause and cardiovascular mortality in elderly men.[61,62] These findings were followed by studies investigating the incidence of CVD and testosterone levels.[63,64] According to these observations, endogenous testosterone appears to exert beneficial effects on the cardiovascular system.

ASSOCIATION OF LOW TESTOSTERONE WITH SURROGATE MARKERS OF ATHEROSCLEROSIS

The mechanisms underlying the epidemiological associations of low testosterone with CVD are complex and poorly understood. However, it is assumed that endogenous testosterone has physiological effects on the blood vessels and exerts atheroprotective effects. Actually, an increasing body of evidence has shown that low levels of endogenous

androgens are associated with atherosclerosis progression in elderly men. Carotid artery intima-media thickness, a common marker of clinical and subclinical atherosclerosis, has been shown to be correlated inversely with testosterone levels.[65–67] Demirbag *et al.*[68] reported a similar finding by examining the intima thickness of the thoracic aorta in older men. Similarly, in the Rotterdam Study population, Hak *et al.*[69] demonstrated that both bioavailable and total testosterone levels were negatively associated with calcified deposits in the abdominal aorta in men older than 55 years of age.

Arterial stiffness, measured as pulse wave velocity or augmentation index, is a predictor of cardiovascular events.[70] Yaron *et al.*[71] reported that age- and blood pressure-adjusted pulse wave velocity was significantly higher in hypogonadal men. Similarly, low testosterone levels in male hemodialysis patients were associated with increases in pulse wave velocity and CVD mortality.[72] Clinical and preclinical evidence exists linking endothelial dysfunction to androgen deficiency. In 187 Japanese men aged 47 ± 15 (s.d.) years, flow-mediated dilatation of the brachial artery, a reliable marker of endothelial function, was positively correlated with plasma testosterone levels, independent of other atherosclerosis risk factors.[73] Comparable results were reported from Europe[74] and specifically from Turkey.[75]

CLINICAL EFFECTS OF ANDROGEN REPLACEMENT THERAPY

As early as the 1940s, Lesser[2] demonstrated that testosterone administration alleviates symptoms and ECG abnormalities in men with angina. Subsequent studies have shown that short-term testosterone administration in men with coronary artery disease results in coronary artery dilation and resistance to ischemia. Indeed, testosterone infusion into the coronary arteries induces vasodilation,[76] and intravenous administration of testosterone reduces the exercise-induced ischemic response in men with stable angina.[77,78] Furthermore, acute administration of testosterone in men with chronic heart failure reduces peripheral vascular resistance and cardiac afterload, resulting in an increased cardiac index.[79] Chronic administration of testosterone also improves functional capacity and symptoms in heart failure patients.[80]

Several reports have shown that testosterone administration improves arterial stiffness and endothelial vasomotor function in men. Testosterone replacement in hypogonadal men results in acute (48 h) and chronic (3 months) decreases in pulse wave velocity.[71] It was also reported that testosterone replacement in men with coronary heart disease and low plasma testosterone decreased radial and aortic augmentation indices.[81] Acute intravenous infusion[82] and 8-week oral administration of testosterone[83] improved flow-mediated vasodilation of the brachial artery.

Testosterone therapy in hypogonadal men with type 2 diabetes mellitus suppressed the production of inflammatory cytokines by circulating monocytes.[84] A randomized, placebo-controlled, double-blind trial of 184 men with hypogonadism and metabolic syndrome showed that intramuscular administration of testosterone undecanoate decreased plasma levels of interleukin-1β, tumor necrosis factor-α and C-reactive protein in association with reductions in body mass index and waist circumference, while interleukin-6 and interleukin-10 did not change significantly.[85]

Taken together, testosterone administration, at least in hypogonadal men, may have a favorable vascular effect, including endothelium-dependent or -independent vasodilation and reduction of arterial stiffness and inflammatory markers. In contrast, the effects of testosterone replacement on the progression of carotid intima-media thickness or other atherosclerotic lesions, as well as on CVD risk,[86] are unknown.

DIRECT EFFECTS OF TESTOSTERONE ON VASCULAR WALLS

Risk factors, such as metabolic syndrome, may partly explain the association of low testosterone with CVD. As the relationship between testosterone and metabolic syndrome has been extensively reviewed,[87,88] this section focuses on the direct effects of testosterone on the vascular wall and the underlying molecular mechanism.

As mentioned above, testosterone therapy can improve vascular function and several markers of atherosclerosis in men. Therefore, vascular ECs, VSMCs and macrophages may be targets of androgen's actions. Indeed, androgen receptor (AR) has been shown to be expressed in these cells.[89–91]

Effects of testosterone on animal models of atherosclerosis and neointima formation

It has been demonstrated that the administration of testosterone in castrated male rabbits that were fed a high-cholesterol diet reduced aortic atherosclerosis, largely independent of plasma lipids.[92,93] In addition, neointima formation after coronary balloon injury in swine was increased by castration and was reversed by testosterone replacement.[94] Regarding the role of AR, conflicting findings have been reported. Nathan *et al.*[95] demonstrated the inhibitory effects of testosterone on fatty streak formation in castrated low-density lipoprotein receptor-deficient male mice, but the effects of testosterone were abrogated by treatment with an aromatase inhibitor, suggesting that estradiol converted from testosterone had a major role. Conversely, Qiu *et al.*[91] showed that nonaromatizable dihydrotestosterone suppressed atherosclerosis formation in castrated male rabbits, indicating a role for AR. Exaggerated vascular remodeling in AR-deficient mice, in response to angiotensin II infusion, also suggests an important role for AR.[96] A recent study by Bourghardt *et al.*[97] may provide a hint in addressing this issue. They administered testosterone in AR-deficient mice with apolipoprotein E-deficient backgrounds and showed that testosterone reduced atherosclerotic lesions, both in AR-deficient and castrated wild-type male mice, but testosterone was less effective in AR-deficient mice, suggesting AR-dependent and -independent mechanisms.

Effects of testosterone on ECs

Several reports have implicated the effects of testosterone on endothelial regeneration. Cai *et al.*[98] demonstrated that testosterone induced time- and dose-dependent proliferation of human aortic ECs via an AR-dependent pathway. In young hypogonadal men, low testosterone levels were associated with a small number of endothelial progenitor cells,[99] and testosterone replacement was able to increase the number of progenitor cells.[100] The synthesis and release of vasoactive substances by EC may have a role in these effects. Of the substances synthesized by EC, NO is a critical molecule that regulates vascular tone and atherosclerosis, and it is a major target of testosterone. It has been reported that testosterone-induced endothelium-dependent vasodilation is mediated in part by NO.[101] We recently demonstrated that testosterone rapidly induces NO production via AR-mediated activation of eNOS in human aortic ECs.[89] Furthermore, we showed that AR directly interacts with the p85 subunit of phosphatidylinositol 3-kinase, resulting in phosphorylation/activation of Akt/eNOS signaling. Taking together with our preliminary observation about the involvement of extracellular signal-regulated kinase 1/2 signaling and [Ca2+]i in AR-dependent eNOS activation, quite similar signaling pathways to those for estrogen can be proposed for testosterone (Figure 1), although some of these pathways should be verified in further studies. The genomic action of testosterone in ECs has not been studied extensively.

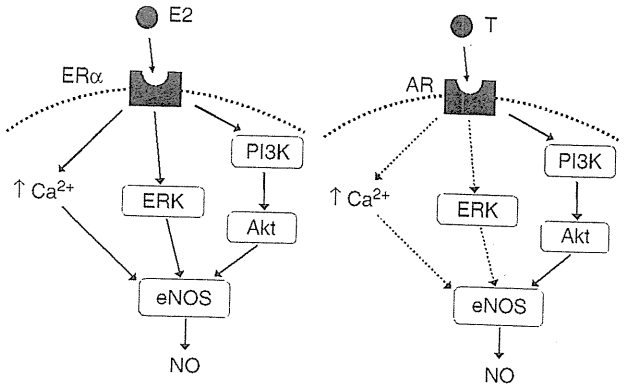

Figure 1 Signal transduction pathways of eNOS activation by estradiol and testosterone in vascular endothelial cells. AR, androgen receptor; E2, estradiol; eNOS, endothelial NO synthase; ERα, estrogen receptor α; ERK, extracellular signal-regulated kinase; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; T, testosterone. Dotted curves indicate the plasma membrane. Dotted arrows indicate probable but undetermined pathways.

It has been reported that testosterone increases the number of ECs secreting endothelin-1,[102] although its contribution to the modulation of vascular tone and of CVD is unknown. Testosterone at physiological concentrations seems to have a beneficial influence on the hemostatic system through tissue plasminogen activator expression and inhibition of plasminogen activator inhibitor type 1 secretion by human umbilical vein ECs.[103]

Effects of testosterone on VSMCs

Most of the rapid vasodilator effects of testosterone are endothelium independent and thus are attributable to its action on VSMCs. In particular, vasodilator responses to pharmacological concentrations of testosterone seem to be AR independent. Yue *et al.*[104] reported that the relaxing response of rabbit coronary arteries to testosterone was significantly inhibited by the potassium-channel inhibitor barium chloride but not by the inhibition of NO synthesis or by removal of the endothelium. Several groups have shown that testosterone inhibits the agonist-induced rise of [Ca2+]i in VSMCs, as has been documented for estrogen. Crews and Khalil[28] reported that testosterone at supra-physiological doses (10–100 pmol l^{-1}) significantly suppresses the vasoconstriction of porcine coronary artery strips induced by prostaglandin F2α or by KCl, in parallel with the inhibition of Ca2+ entry. Hall *et al.*[105] demonstrated, using the A7r5 VSMC cell line, that testosterone and dihydrotestosterone selectively suppressed Ca2+ entry via L-type Ca2+ channels. Similar results have been reported in different experimental conditions by other groups.[106–108]

The involvement of potassium channels in testosterone-induced vasodilatation has also been studied by many researchers.[109–111] Cairrao *et al.*[112] reported that an AR antagonist, flutamide, and an adenosine triphosphate-sensitive potassium-channel inhibitor, glibenclamide, had no influence on the testosterone relaxant effect, whereas a voltage-sensitive potassium-channel inhibitor, 4-aminopyridine, decreased this effect of testosterone. Opening of voltage-sensitive potassium channels induces hyperpolarization of the plasma membrane, which in turn may lead to the closing of L-type Ca2+ channels. These pharmacological studies, most of which used chemical inhibitors, may be strengthened by studies employing molecular-targeting strategies.

Accumulation of VSMCs in damaged vascular layers is a critical process in the development of atherosclerosis and is closely related to hypertension and its complications. Many, but not all, of the previous studies indicated that testosterone might inhibit VSMC growth. Hanke *et al.*[113] reported, using an *ex vivo* organ culture system, that testosterone at 10–100 ng ml^{-1} significantly inhibited neointima formation in association with increased expression of AR in endothelium-denuded rabbit aortic rings after 21 days of incubation. Somjen *et al.*[114] demonstrated the dose-dependent inhibitory effects of dihydrotestosterone and membrane-impermeable testosterone on DNA synthesis in cultured VSMCs derived from the human umbilical artery, suggesting a role for membrane AR. The above-mentioned study by Tharp *et al.*[94] showed that the expressions of protein kinase C delta and p27 (kip1) were increased in coronary artery sections of testosterone-treated swine.

Androgen-responsive genes directly regulated by AR in VSMCs have not been determined, except for AR itself. However, we recently found that growth arrest-specific gene 6 was transactivated by testosterone in human VSMCs via binding of AR to the promoter region of the growth arrest-specific gene 6.[90] In this study, testosterone inhibited inorganic phosphate-induced VSMC apoptosis, leading to the suppression of VSMC calcification. To further elucidate the mechanism underlying the effects of testosterone on the cardiovascular system, identification of androgen-responsive genes in VSMCs, as well as in ECs, is required in future studies.

Natoli *et al.*[115] investigated, using human aortic VMSCs, and found that testosterone significantly reduced collagen and fibrillin-1 deposition, while it had no effect on elastin. They also found that testosterone increased the expression of matrix metalloproteinase-3, which has an important role in vascular remodeling.

POSSIBLE HARMFUL EFFECTS OF TESTOSTERONE ON BLOOD VESSELS

Although many studies have shown the beneficial effects of testosterone on the blood vessels, as mentioned above, other studies have suggested that long-term administration of testosterone may elicit harmful effects, especially vasoconstriction via upregulation of thromboxane A2,[116] norepinephrine synthesis,[117] angiotensin II[118] and endothelin-1.[102] It has been also reported that testosterone accelerates vascular remodeling[119] and stimulates renal prohypertensive processes, including the renin–angiotensin–aldosterone system.[120] Recent meta-analyses have revealed that CVD events were not different between testosterone and placebo groups,[86,121] indicating the complexity of testosterone therapy, as was shown for estrogen therapy in women.

TESTOSTERONE DEFICIENCY AND CVD IN WOMEN

An age-related reduction in circulating levels of androgens occurs in women as well.[122] However, it is unclear whether this decline adversely affects vascular health in women. Higher serum testosterone concentrations, within the physiological range, have been associated with lower carotid intima-media thickness,[123] suggesting potential protective effects of endogenous testosterone on cardiovascular health in pre- and postmenopausal women. Conversely, it is well known that women with polycystic ovary syndrome, who exhibit high androgen levels, are at a higher risk for CVD. Some studies have reported that high testosterone is associated with an adverse CVD risk factor profile in postmenopausal women, irrespective of polycystic ovary syndrome.[3,124] Polymorphism of the (CAG)n repeat of the AR gene was associated with CVD and risk factor profiles in postmenopausal women.[125] Thus far, evidence is lacking for an association of testosterone with CVD events in women, and it is uncertain whether testosterone could be used as a postmenopausal hormone therapy.

CONCLUSION

In this review, we illustrated the sex hormones' effects on the cardiovascular system, focusing on the action of testosterone on the blood vessels. Endogenous androgens, as well as estrogen, may display favorable effects on the vasculature, but whether HRT protects aging men and women from CVD is still unknown. Although testosterone administration seems to have diverse or contradictory effects in younger men and women, androgen therapy may provide hope for elderly hypogonadal men. This issue will remain unclear unless clinical trials of testosterone therapy are conducted. Also, progress in basic research on hormonal effects on blood vessels is essential to understanding the role of sex hormones in the development of CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants received from Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Culture and Sports of Japan (21390220, 20249041).

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Geriatr Gerontol Int 2011

ORIGINAL ARTICLE

Polypharmacy as a risk for fall occurrence in geriatric outpatients

Taro Kojima,[1] Masahiro Akishita,[1] Tetsuro Nakamura,[2] Kazushi Nomura,[1] Sumito Ogawa,[1] Katsuya Iijima,[1] Masato Eto[1] and Yasuyoshi Ouchi[1]

[1]*Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, and* [2]*Research Institute of Aging Science, Tokyo, Japan*

Objective: To investigate the predictors of falls, such as comorbidity and medication, in geriatric outpatients in a longitudinal observational study.

Methods: A total of 172 outpatients (45 men and 126 women, mean age 76.9 ± 7.0 years) were evaluated. Physical examination, clinical history and medication profile were obtained from each patient at baseline. These patients were followed for up to 2 years and falls were self-reported to their physicians. The factors associated with falls were analyzed statistically.

Results: A total of 32 patients experienced falls within 2 years. On univariate analysis, older age, osteoporosis, number of comorbid conditions and number of drugs were significantly associated with falls within 2 years. On multiple logistic regression analysis, the number of drugs was associated with falls, independent of age, sex, number of comorbid conditions and other factors that were significantly associated in univariate analysis. A receiver–operator curve evaluating the optimal cut-off value for the number of drugs showed that taking five or more drugs was a significant risk.

Conclusion: In geriatric outpatients, polypharmacy is associated with falls. Intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidity and falls. **Geriatr Gerontol Int 2011; ••: ••–••.**

Keywords: bone/musculo-skeletal, elderly, falls, geriatric medicine, internal medicine, polypharmacy.

Introduction

Previous studies have assessed the risk factors for falls in community-dwelling elderly,[1–3] but not in geriatric outpatients, and history of falls, physical ability and living environment were found to be predictors of falls. Outpatients have different characteristics from community-dwelling elderly, and previous studies have not assessed whether medical comorbidity and therapeutic drugs might be risk factors for falls. Falls in patients on medication are complicated, because some drugs, such as aspirin, can cause serious bleeding when they have injurious falls, and others, such as antihypertensive[4] and hypoglycemic[5,6] agents, can cause falls.

Previously, we reported that polypharmacy was associated with the tendency for falls using four indices of fall tendency in a cross-sectional setting in geriatric outpatients,[7] though that study did not evaluate fall occurrences, and also not in a longitudinal manner. Therefore, we aimed at investigating whether polypharmacy was predictive of fall occurrences in a prospective fashion. For this purpose, we followed geriatric outpatients for up to 2 years, and assessed whether polypharmacy is a risk for fall occurrence, together with other risks.

Accepted for publication 19 October 2011.

Correspondence: Dr Masahiro Akishita MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: akishita-tky@umin.ac.jp

doi: 10.1111/j.1447-0594.2011.00783.x

The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver–operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

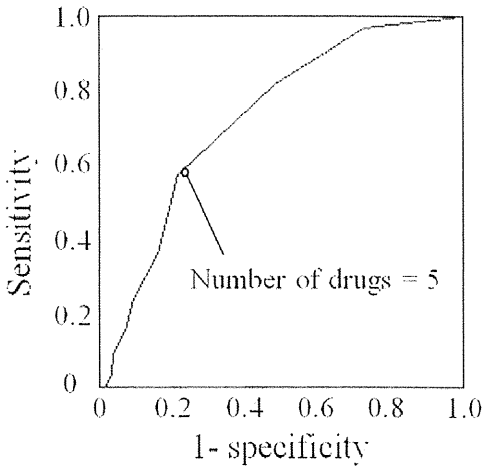

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

Acknowledgment

We thank Ms Fumie Tanaka for her excellent technical assistance. This study was financially supported by grants from the Ministry of Health, Labour and Welfare of Japan (H21-Chouju-Ippan-005, H22-Chouju-Shitei-009).

Disclosure statement

The authors declare no conflict of interest.

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Geriatr Gerontol Int 2011; 11: 438–444

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of polypharmacy with fall risk among geriatric outpatients

Taro Kojima,[1] Masahiro Akishita,[1] Tetsuro Nakamura,[2] Kazushi Nomura,[1] Sumito Ogawa,[1] Katsuya Iijima,[1] Masato Eto[1] and Yasuyoshi Ouchi[1]

[1]*Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, and* [2]*Research Institute of Aging Science, Tokyo, Japan*

Aim: To investigate the association of fall risk with comorbidities and medications in geriatric outpatients in a cross-sectional design.

Methods: A total of 262 outpatients (84 men and 178 women, mean age 76.2 ± 6.8 years) were evaluated. Physical examination, clinical histories and medication profile were obtained from each patient. History of falls in the past year, 22-item fall risk index, 13-point simple screening test for fall, and time interval of one-leg standing test were examined as markers of fall risk.

Results: On univariate analysis, older age, female sex, hypertension, osteoporosis, history of stroke, number of comorbidities, use of antihypertensives, aspirin, bisphosphonates, hypnotics and number of prescribed drugs were significantly associated with either of four indices. On multiple regression analysis, the number of drugs was associated with all of the four indices, independent of other factors associated in the univariate analysis. The association of number of drugs with fall risk indices was stepwise.

Conclusion: In geriatric outpatients, polypharmacy rather than number of comorbidities was associated with fall risk. Prospective and intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidities and fall risk. **Geriatr Gerontol Int 2011; 11: 438–444.**

Keywords: elderly, fall, polypharmacy, risk factors.

Introduction

Falls occur in more than 10% per year of community-dwelling elderly people,[1–3] and approximately 10% of falls lead to bone fracture. Also, falls are reported to be the third leading cause of a bedridden state among the elderly.[4] Previous studies assessed the risk factors of falls in community-dwelling elderly,[5–7] and history of falls, physical ability and living environment were found to be predictors of fall risk. However, these studies have not sufficiently assessed medical comorbidities and therapeutic drugs as risk factors of falls, although many elderly subjects have chronic illness such as hypertension, diabetes, cardiovascular diseases, osteoporosis and insomnia. Falls in patients on medications are more complicated, because some drugs such as aspirin could cause serious bleeding when they have injurious falls, and others such as antihypertensives[8] and hypoglycemic agents[9,10] could cause falls. Therefore, it is important to evaluate the association between fall risk and medical comorbidities or therapeutic drugs. Multiple drug use or polypharmacy is frequently seen in elderly patients because most of them have multiple chronic diseases to be treated. Moreover, inappropriate drug use is frequently seen in patients with polypharmacy.[11]

In Japan, a 22-item fall risk index questionnaire covering physical, cognitive, emotional and social aspects of

Accepted for publication 3 March 2011.

Correspondence: Dr Masahiro Akishita MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: akishita-tky@umin.ac.jp

 doi: 10.1111/j.1447-0594.2011.00703.x

functioning and environmental factors was established.[7] Also, by evaluating the validity of this questionnaire in community-dwelling older people, a simple screening test consisting of five items and total of 13 points was constructed.[2] Using these questionnaires and one-leg standing test[12] as indices of fall risk, we investigated the association of fall risk with comorbidities and medications in geriatric outpatients.

Methods

Patients

A total of 262 consecutive outpatients aged 65 years or older were enrolled who were referred for the treatment of chronic diseases such as hypertension, dyslipidemia, diabetes and osteoporosis every 2–4 weeks at a geriatric clinic located in Tokyo, Japan. All the patients were able to walk independently and were in stable conditions. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information were obtained including past history of stroke, myocardial infarction and malignancy. All the medical information including diagnoses and the prescribed drugs were obtained from the medical chart recorded by their physicians in charge. The patients whose prescriptions were changed within 1 month before enrollment were excluded. Accordingly, the included subjects had been taking the same drugs for at least 1 month before enrollment.

Ethical consideration

This study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Four indices of fall tendency

On the day of the enrollment, all patients were examined for four indices to investigate the fall risk: (i) history of fall in the past year (no or yes); (ii) a 22-item portable fall risk index questionnaire developed by the working group of the Ministry of Health, Labor and Welfare (see Appendix I);[7] (iii) 13-point simple screening test to assess the risk of fall which was also developed by the same working group (see Appendix II);[2] and (iv) duration time of open-eye one-leg standing test.

Table 1 Characteristics of study subjects

Age			76.2 ± 6.8 years old
Male	32.1%	(n = 84)	75.3 ± 6.6 years old
Female	67.9%	(n = 178)	76.6 ± 6.8 years old
Comorbidities			
Hypertension	64.1%	(n = 168)	
Dyslipidemia	47.7%	(n = 125)	
Diabetes	18.7%	(n = 49)	
Osteoporosis	24.0%	(n = 63)	
History of stroke	6.5%	(n = 17)	
History of myocardial infarction	3.4%	(n = 9)	
History of cancer	5.3%	(n = 14)	
Number of comorbidities	1.90 ± 1.09		
Drug use			
Antihypertensive use	57.6%	(n = 151)	
Calcium channel blockers	39.3%	(n = 103)	
Angiotensin-II receptors blockers	34.7%	(n = 91)	
Beta-blocker	6.9%	(n = 18)	
Angiotensin converting enzyme inhibitors	5.7%	(n = 15)	
Diuretics	5.0%	(n = 13)	
Statins	24.4%	(n = 64)	
Sulfonylureas	6.5%	(n = 17)	
Aspirin	20.6%	(n = 54)	
Vitamin D	4.6%	(n = 12)	
Bisphosphonates	6.5%	(n = 17)	
H_2-blockers	9.9%	(n = 26)	
Proton pump inhibitors	6.5%	(n = 17)	
Hypnotics	18.3%	(n = 48)	
Number of drugs	3.4 ± 2.8		

Values are expressed as mean ± standard deviation.