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Author Contributions: Paul Regal designed the study, assessed patients, served on the consensus panel, analyzed the data, and wrote the article. Eileen Heatherington performed cognitive tests and was a panel member for consensus diagnosis of dementia.

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FACTORS ASSOCIATED WITH PROLONGED HOSPITAL STAY IN A GERIATRIC WARD OF A UNIVERSITY HOSPITAL IN JAPAN

To the Editor: We read with interest the article by Lakhan and colleagues,[1] which showed the high prevalence and worsening of geriatric syndrome during acute care hospitalization. Because falls, incontinence, impairment in activities of daily living (ADLs), and other geriatric syndrome components increase the care burden and limit discharge planning in acute care hospitals, geriatric syndrome might cause prolonged hospital stays. A prolonged hospital stay is one of the major determinants of medical cost and is thus a serious problem in geriatric medicine. Previous studies have shown that clinical events during hospitalization,[2,3] basic ADLs,[4] and nonmedical factors such as delayed transfer to a nursing facility or disagreement on the discharge plan among family members[5] are risk factors for prolonged hospital stay. Furthermore, because older adults have multiple comorbid conditions and are susceptible to adverse drug reactions (ADRs), these factors might be related to length of hospital stay. To test this hypothesis, the association between geriatric conditions such as geriatric syndrome, ADLs, and ADRs and prolonged hospital stay were comprehensively investigated using the database of the geriatric ward of the University of Tokyo Hospital from 1995 to 2010. The ethics committee of the Graduate School of Medicine, University of Tokyo approved this study.

All records of patients aged 65 and older from 1995 to 2010 were reviewed. Data on length of stay, acute hospitalization, ADRs, body mass index (BMI), number of diseases and drugs, geriatric syndrome, and Barthel Index were collected. Twenty-three components of geriatric syndrome such as falls, cognitive impairment, urinary incontinence, constipation, and insomnia were included in the analysis. Records lacking information on any of the variables were excluded. Cases of scheduled short-term hospitalization were excluded. Finally, the records of 1,616

Table 1. Characteristics of Study Patients and Analyses for Length of Hospital Stay (N = 1,616)

Characteristic	Value	Univariate Analysis (R or Hospital Stay, Days, Mean ± SD)	Standardized Regression Coefficient
Age, mean ± SD	78.3 ± 7.0	0.001	−0.099[d]
Sex, *n* (%)			
Female	778 (48.1)	26.8 ± 20.2	
Male	838 (51.9)	27.6 ± 24.6[a]	
Acute hospitalization, *n* (%)			
Yes	300 (18.5)	26.2 ± 21.0	
No	1,316 (81.5)	31.8 ± 28.2[a,d]	
Adverse drug reaction, *n* (%)			
Yes	190 (11.8)	26.4 ± 19.5	0.078[c]
No	1,426 (88.2)	33.3 ± 38.1[a,d]	
Body mass index, kg/m^2, mean ± SD	22.0 ± 4.1	−0.59[d]	−0.062[b]
Barthel Index (points out of 100), mean ± SD	83.1 ± 26.1	−0.178[d]	−0.13[d]
Number of diseases, mean ± SD	5.3 ± 2.3	1.43[c]	0.082[c]
Number of drugs, mean ± SD	6.8 ± 3.6	0.411[b]	–
Number of geriatric syndrome components, mean ± SD	4.6 ± 3.6	1.66[d]	0.19[d]

All data were collected soon after admission. For sex, acute hospitalization, and adverse drug reactions, a simple *t*-test was performed for univariate analysis, and values are expressed as mean ± standard deviation (SD).

[a]*P*-values are for comparison to female or no. Pearson correlation coefficients (R) are shown for the remaining factors in univariate analysis. All variables shown were included in stepwise regression analysis, and factors significantly associated were analyzed in multiple regression analysis (coefficient of determination = 0.32).

[b]$P < .05$.

[c]$P < .005$.

[d]$P < .001$.

patients were analyzed (mean age 78.3 ± 7.0, 52% male). All data were obtained soon after admission. Values are expressed as means ± standard deviations and were analyzed using JMP version 9.0.2 (SAS Institute, Inc., Cary, NC). $P < .05$ was considered statistically significant.

Mean length of stay was 27.3 ± 22.6 days (range 1–322 days). The results of univariate and multivariate analyses for length of stay are shown in Table 1. Multiple stepwise regression analysis showed that ADRs, number of diseases, and number of geriatric syndrome components were positively associated with longer hospital stay, whereas age, BMI, and Barthel Index were negatively associated. The number of geriatric syndrome components was significantly associated with hospital stay independent of number of diseases.

The present analysis demonstrated that geriatric factors such as ADRs, multiple diseases, low BMI, ADL dependence, and number of geriatric syndrome components were associated with longer hospital stay in a large group. The finding that ADRs are a risk for prolonged hospital stay is consistent with a previous report,[6] and ADL dependence has been reported as a risk in a smaller group.[4] Furthermore, the number of geriatric syndrome components and undernutrition were risk factors for prolonged hospital stay in a large-scale study. Frailty, which is also known to be a risk factor,[7] was not examined independently in the present study, but ADL dependence and undernutrition, both of which are major components of frailty, were found to be risk factors, so it is reasonable to assume that frailty was associated with length of hospital stay in the current cohort as well. The present study revealed that the accumulation of geriatric syndrome components was a risk factor for prolonged hospital stay independent of multiple diseases and, presumably, frailty. Thus, geriatric syndrome should be comprehensively managed during hospitalization. The reason for the negative association between age and length of stay is unclear, but the presence of young-old patients with disability or complicated conditions on the geriatric ward might have influenced the results.

In summary, the present study provides new insight into the significance of geriatric conditions in relation to prolonged hospital stay in older adults. ADL dependence, undernutrition, ADRs, and geriatric syndrome should be carefully assessed and interventions provided when caring for older inpatients.

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ACTIVITIES OF DAILY LIVING RATHER THAN DEPRESSIVE SYMPTOMS INCREASE THE RISK OF MORTALITY IN JAPANESE COMMUNITY-DWELLING ELDERLY PEOPLE: A 4-YEAR LONGITUDINAL SURVEY

To the Editor: The article entitled "Depressive Symptoms Increase the Risk of Mortality in Older Mexican Community-Dwelling Adults" by Piña-Escudero et al.[1] deeply impressed us. Although it has been shown that older adults with depressive symptoms (DSs) have fewer quality-adjusted life years than those with chronic medical conditions,[2] Piña-Escudero et al. in their 2-year longitudinal study, showed that DSs increase mortality risk regardless of multiple covariates such as medical conditions and disability in activities of daily living (ADL). Similarly, results of a meta-analysis of 25 studies suggest that depression increases the risk of mortality,[3] although those studies did not assess ADL in detail. The risk of mortality in Japanese community-dwelling elderly people is reported herein, focusing on DSs and ADLs in a 4-year longitudinal survey.

The study population included 1,818 community-dwelling individuals aged 65 and older in Tosa Town, Japan; 1,600 (88.0%) participants who completed self-reported geriatric questionnaires in 2006 were included in the study. The questionnaires consisted of questions on ADLs and the 15-item Geriatric Depression Scale (GDS-15).[4] For ADL assessment, participants rated their

RELATIONSHIP BETWEEN TESTOSTERONE AND COGNITIVE FUNCTION IN ELDERLY MEN WITH DEMENTIA

To the Editor: A decrease in sex hormones with aging has been reported to be related to psychosomatic disorders such as late-onset hypogonadism syndrome, frailty, and cognitive impairment in adult men.[1] For example, a community-based cross-sectional study has shown that elderly men with a lower blood concentration of bioavailable testosterone have more-severe impairment of cognitive function.[2] Moreover, a longitudinal study indicated that serum free testosterone (FT) concentration could predict memory performance and cognitive status in elderly men,[3] but it is unknown whether lower testosterone concentration is related to cognitive impairment in individuals with dementia, because the previous studies primarily focused on a healthy community-based population. Also, few studies have addressed the relationship between testosterone and cognitive function in elderly Japanese men.

One recent cross-sectional study showed that total testosterone and FT concentration were associated with activities of daily living (ADLs) in institutionalized elderly men.[4] This study also revealed that a relationship between testosterone and cognitive function could be found even in institutionalized elderly men with physical or neuropsychiatric dysfunction. Thus, whether lower testosterone concentration is related to deterioration of ADL in elderly men with cognitive impairment was longitudinally investigated.

Fifty-two male outpatients attending the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were recruited (mean age 77.0 ± 5.5, range 65–87). Participants' clinical backgrounds were hypertension, 48.9%; diabetes mellitus, 12.2%; and dyslipidemia, 38.1%. None had a history of stroke. Comprehensive geriatric assessment was performed based on basic ADLs (Barthel Index),[5] instrumental ADLs (Lawton and Brody IADLs, 0–5 points in men),[6] cognitive function (Mini-Mental State Examination (MMSE)),[7] mood (Geriatric Depression Scale (GDS), 15 items),[8] and vitality (Vitality Index, 10-point scale).[9] This assessment was repeated 1, 2, and 3 years after baseline assessment at the first visit to the clinic. At the first visit, blood was drawn after an overnight fast and FT concentration was measured using radioimmunoassay. FT values ranged from 1.0 to 53.0 pmol/L (mean ± SD 30.4 ± 11.0 pmol/L). Participants were classified into three groups according to tertile according to the baseline FT value (Figure 1), and the parameters from the comprehensive geriatric assessment were compared between groups and visits. Statistical data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). One-way analysis of variance (ANOVA) was applied for comparisons between groups, and the Fisher post hoc test was applied when significant ($P < .05$). One-way repeated ANOVA was used for comparisons between baseline and the 1-, 2-, and 3-year visits, and the Fisher post hoc test was applied when significant ($P < .05$).

There were no significant differences between groups in age (high, 75.3; middle, 76.6; low, 79.0), basic ADLs (high, 96.9; middle, 99.1; low, 95.3 points), MMSE (high, 23.2; middle, 25.1; low, 23.1 points), GDS-15 (high, 5.1; middle, 4.1; low, 4.6 points), and Vitality Index (high, 9.1; middle, 9.1; low, 8.8 points) at baseline, whereas IADLs tended to be lower (high, 4.1; middle, 4.1; low, 3.4 points, $P = .06$) in the low FT tertile group than in the other groups.

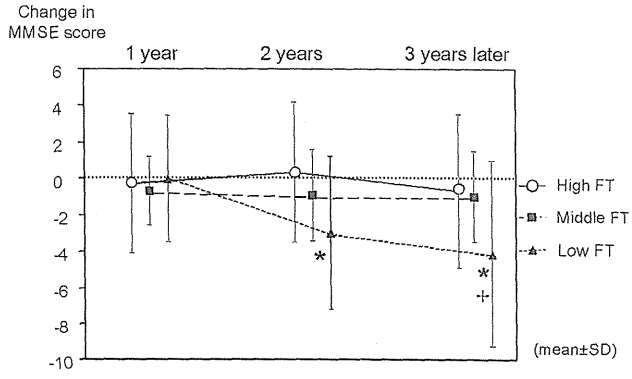

Figure 1. Change in Mini-Mental State Examination (MMSE) score according to tertile of serum free testosterone (FT) level in men. FT tertile: high, >36.1 pmol/L, n = 17; middle, 29.1–35.4 pmol/L, n = 17; low, <28.8 pmol/L, n = 18. *$P < 0.05$ vs highest FT group, +$P < 0.05$ vs middle FT group.

At the 1-year visit, there was no difference in change in MMSE score from baseline between the groups, although the decrease in MMSE score was larger in the low FT tertile group than in the middle and high tertile groups at the 2- and 3-year visits (Figure 1). Also, MMSE scores were lower in the low FT tertile group at the 2- ($P = .009$) and 3-year ($P < 0.001$) visits than at baseline, whereas they were not lower in the middle and high tertile groups. In contrast, there was no such trend in basic ADLs, IADLs, GDS scores, and Vitality Index.

Multiple regression analysis was performed with a decrease in MMSE score as a dependent variable and age; ADLs; body mass index; presence of hypertension, diabetes mellitus, or hyperlipidemia; and FT concentration as independent variables to consider factors affecting cognitive impairment, according to a previous report.[4] Blood FT concentration was found to be an independent predictor of decrease in MMSE score at the 3-year visit ($\beta = 0.492$, $P = .02$).

A number of investigations support the biological plausibility of a protective effect of testosterone against cognitive dysfunction. The present findings from memory clinic outpatients are consistent with previous findings observed in elderly community-based men, showing a relationship between FT concentration and cognitive performance.[3] Furthermore, the present findings indicate that a lower FT concentration could lead to a faster decline in cognitive function in elderly Japanese men who already show cognitive impairment. This study provides fundamental data for the future study of hormone replacement therapy for cognitive decline in elderly adults with low FT.

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BASELINE INSTRUMENTAL ACTIVITIES OF DAILY LIVING AND INCIDENT DEMENTIA

To the Editor: Sikkes et al.[1] have written an important paper showing that individuals without dementia with impairment in at least one of nine instrumental activities of daily living (IADLs) at baseline had a significantly higher incidence of dementia at 12 months (24.4%) than individuals without IADL impairment at baseline (16.7%) (P = .04). Their 531 participants who were followed for 12 months were relatively young (mean age 69.6), so it was decided to duplicate their study from prospective data from the Wyong Hospital Memory Clinic, 100 km north of Sydney. From 415 individuals attending a memory clinic, community-dwelling individuals aged 60 and older who were free of dementia at baseline and had a Mini-Mental State Examination score (MMSE[2]) of 25 to 30 and a follow-up MMSE and Montreal Cognitive Assessment (MoCA), range 0 (worst) to 30 (best)[3] at 12 months were selected in a consensus conference of a geriatrician (PJ) and a clinical nurse consultant (EH). Each individual's family rated IADLs on the Nottingham scale,[4] which ranged from 0 (worst) to 22 (best). Twenty-two of 82 (27%) converted to dementia at 12 months, compared with Sikkes conversion rate of 20.8% at 24 months—the most likely reason for this difference was that mean age (79.1) was 9.5 years older than theirs (69.6). Stats Direct Version 2.7.8b (StatsDirect Ltd, Altrincham, UK) from November 2011 was used to compare converters and nonconverters. Mean age of the 22 converters at baseline was significantly higher that that of the 60 nonconverters (82.0 ± 5.8 vs 78.0 ± 6.8, P < .01), mean IADL score at baseline was significantly lower (13.1 ± 5.3 vs 16.1 ± 4.0, P = .0236), MMSE score at baseline was by definition lower (25.6 ± 0.73 vs 27.5 ± 1.50, P < .001), and MoCA score at baseline was lower (19.2 ± 3.5 vs 22.8 ± 3.9, P < .001). At 12 months, IADL (11.4 ± 5.6 vs 15.4 ± 4.5, P = .004), MMSE score (21.6 ± 4.5 vs 27.4 ± 1.6, P < .001), MoCA (16.8 ± 3.6 vs 22.8 ± 4.2, P < .001) remained significantly lower in converters.

The Nottingham IADL covers seven of the nine IADL items that Sikkes used, excluding medications and finances. Women are more likely than men to perform five of the Nottingham IADL items unless the men live alone with no home care services: cleaning the kitchen, making a hot snack, washing small items of clothing, doing a full clothes wash, and doing housework.

Although the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for dementia include a decline in social and occupational function, there is a surprising lack of research into IADLs as a predictor of incident dementia. This is an important topic for future research and ongoing studies are being conducted in three cohorts: Wyong Memory Clinic; general medical inpatients with delirium or subsyndromal delirium—a prospective randomized controlled trial, Central Coast Australia Delirium Intervention Study; and PhD study, PR DEFEAT DELIRIUM, in outpatients at high risk for incident delirium. One study[5] with 255 community-dwelling individuals attending a memory clinic who were followed an average of 13 months has been published. The 11.4% of participants with antithyroid antibodies had similar outcomes at 12 months with respect to IADLs, decline in IADLs, MMSE and MoCA scores, and transfer to residential care.

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Disclosure

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High risk of adverse drug reactions in elderly patients taking six or more drugs: Analysis of inpatient database

Dear Editor,

Polypharmacy is frequently seen in elderly patients, largely because of the existence of multiple comorbid conditions. All medications have the potential for harm as well as benefit, and thus, physicians must make difficult trade-offs between both sides of guideline-directed care.[1,2] Some drugs are reported to increase adverse drug reactions (ADR), and have been listed as potentially inappropriate medications (PIM), which should not be used generally in elderly patients.[3–5] However, it is still complicated for general practitioners to check PIM for each patient. As polypharmacy is a well-known risk for ADR,[6,7] and the frequency of PIM use rises sharply according to the number of drugs,[7] the optimal number of drugs defining polypharmacy might be of substantial help for physicians. Therefore, we aimed to determine the cut-off number of drugs in relation to ADR using the inpatient database of our geriatric department.

All records of patients aged 65 years or older who were admitted to the Department of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan, from 1995 to 2010 were reviewed. Retrospective use of the patient database was approved by the ethics committee of The University of Tokyo. Records lacking information on ADR or the number of drugs and patients taking no drugs were excluded. Finally, we analyzed the records of 2412 patients (mean ± SD age = 78.7 ± 7.3 years, male 51.3%). ADR was defined as unintended or undesired harmful effects presumably caused by drugs. The occurrence of ADR was assessed before discharge by the physician in charge, and other data were obtained soon after admission. Odds ratios with 95% confidence intervals for ADR were obtained by logistic regression analysis. The receiver operating characteristic (ROC) curve was assessed to define the optimal number of drugs in relation to ADR. Data were analyzed using JMP version 9.0.2 (SAS Institute, Cary, NC, USA).

The number of prescribed drugs per patient was 6.6 ± 3.6 (mean ± SD; range = 1–30), and ADR were observed in 252 patients (10.5%). Patients with ADR were taking more drugs than those without ADR (7.6 ± 3.8 *vs* 6.4 ± 3.5 drugs, $P < 0.0001$ by unpaired *t*-test). ADR was significantly associated with the number of drugs in unadjusted and age- and sex-adjusted logistic regression analysis (data not shown). When ADR were analyzed according to the number of drugs by quintile, the odds ratio of ADR was significantly higher in the groups taking six or more drugs (Fig. 1). Furthermore, ROC analysis showed that the optimal cut-off number of drugs was six, although the sensitivity of 0.560 and specificity of 0.710 were not high, with a small area under the curve of 0.591.

Previously, elderly outpatients taking five to eight drugs were reported to be at greater risk of ADR-related hospitalization than those taking zero to four drugs.[6] Also, we have reported that taking five or more drugs is a risk factor for falls in outpatients.[8] Taking these findings together, it might be reasonable to consider six or more drugs as the cut-off of polypharmacy in terms of ADR in elderly patients. The present study had some limitations; the results were obtained from inpatients managed by geriatricians, and thus might not extend to general outpatients. Next, this database did not have information for types of ADR; so they could not be clarified in detail in the present. According to our previous study, hematological, neurological and

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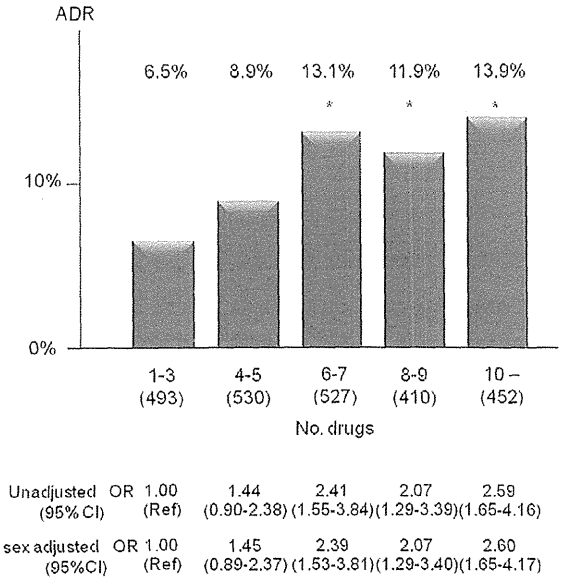

Figure 1 Frequency of adverse drug reactions according to quintile of number of prescribed drugs. Unadjusted and age-sex adjusted odds ratios (95% confidence interval) of adverse drug reactions are shown. $^*P < 0.05$ versus one to three drugs. OR, odds ratio.

cardiovascular events were reported to be more frequent than ADR in elderly inpatients,[9] and so, these are possibly the major types in the present study. Also, ROC analysis did not fit well for the present cohort.

In summary, the present study provided the cut-off number of drugs for screening of elderly patients at high risk of ADR. Prospective studies and intervention studies examining the effect of drug reduction on ADR and comorbid conditions are required to confirm this finding.

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C-kit-positive acute myelogenous leukemia effectively treated with imatinib: A case report and review of the literature

It is highly advisable to choose a strategy to improve the quality of life (QOL), rather than a curative strategy, such as conventional chemotherapy, for very elderly patients with acute myelogenous leukemia (AML). Molecular targeted therapy might also be considered as an important strategy to take into account.[1]

An 88-year-old man was referred to Juntendo University Urayasu Hospital in Chiba, Japan, because of fever and headache in April 2004. The spleen was enlarged to 5 cm below the left costal margin. White blood cell (WBC) count was $61.1 \times 10^4/\mu L$, with 29% blasts and 6.5% basophils. Other data were hemoglobin (Hb) 10.6 g/dL, platelet (plt) $41.0 \times 10^4/\mu L$, lactate dehydrogenase (LDH) 685 IU/L, uric acid (UA) 10.0 mg/dL and C-reactive protein (CRP) 14.6 mg/dL. Bone marrow was myeloid hyperplasia with 27% blasts. Flow cytometer showed that the leukemic cells were positive for myeloperoxidase, CD7, CD13, CD15, CD33, CD34 and c-kit (CD117). Because the leukocytosis with blasts, mild basophilia and splenomegaly resembled blast crisis of chronic myeloid leukemia, and furthermore the patient was very old, imatinib 600 mg daily was tried. Fortunately, imatinib was effective before chromosome analysis later showed trisomy 8. Although the rate of blasts in the peripheral WBC was almost constant, the number of WBC decreased and red blood cells transfusion (RBCT) was not required soon. The patient could leave hospital on day 28 and he had a good QOL. On day 90, the WBC count was 5000/μL with 28% blasts, and Hb and plt were stable; furthermore, the spleen was not palpable. Although generalized edema and pleural effusion occurred as side-effects of imatinib on day 110, they improved with furosemide. However, on day 130, the number of WBC gradually increased,

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LETTERS TO THE EDITOR

Gastrointestinal hemorrhage and antithrombotic drug use in geriatric patients

Dear Editor,

Recent guidelines recommend the aggressive use of antithrombotic medications in patients at high risk of thrombotic events. Although the risk of thrombosis increases with age, critical bleeding related to antithrombotic drug use is frequently seen in older patients.[1] Thus, guideline-directed use of antithrombotic medications might cause more harm than benefits among older patients with multiple comorbid conditions.[2,3] To increase the benefit-to-harm ratio, geriatricians might take care to stratify the risks and totally manage the patients. We hypothesized that such geriatricians' approaches lead to harmless use of antithrombotic medications. For this purpose, we carried out a case–control study to investigate the association between gastrointestinal hemorrhage and antithrombotic drug use.

We analyzed the inpatient registry of the Department of Geriatric Medicine, University of Tokyo Hospital between 1996 and 2007 (2249 patients) to identify patients ≥60 years-of-age who were admitted to the department as a result of gastrointestinal hemorrhage. The database was searched using the keywords of gastrointestinal hemorrhage, melena, hematemesis and anemia. Then, medical records of the extracted patients were reviewed. Finally, a total of 47 patients were defined to fulfil the criteria. Next, using risk-set sampling, we selected four controls per case matched for age, sex and the timing of hospitalization from the same inpatient registry. The data were obtained on prescriptions of antithrombotic drugs (aspirin, warfarin, cilostazol and ticlopidine) and anti-ulcer drugs (proton pump inhibitors and H2 blockers), and comorbid conditions.

Among the cases, causes of gastrointestinal hemorrhage were ulcer (48.9%), cancer (8.5%), ischemic colitis (6.3%), colon diverticulum (4.2%), Mallory–Weiss syndrome (4.2%) and hemorrhoid (2.1%), and 21.2% remained uncertain. As shown in Table 1, 17 cases and 71 controls were taking antithrombotic drugs. Of them, aspirin was most frequently prescribed both in case and control groups. There was no significant difference between case and control groups in the prescription rate of antithrombotic drugs ($\chi^2 = 0.20$, $P = 0.65$) and that of aspirin ($\chi^2 = 0.43$, $P = 0.51$). Furthermore, unadjusted logistic regression analyses showed that antithrombotic drug use and antiulcer drug use was not associated with gastrointestinal hemorrhage. The odds ratio of antithrombotic drug use for gastrointestinal hemorrhage was 0.91 (95% CI 0.46–1.81) after adjustment by age, sex and anti-ulcer drug use. Exclusion of the patients with cancer-related hemorrhage did not fundamentally influence the analytical results (data not shown).

This small case–control study showed no association of admission as a result of gastrointestinal hemorrhage with the use of antithrombotic drugs or aspirin among older patients. As most of the patients were managed by geriatricians in our department, the finding might be limited to the particular facility or cohort, but might not be extended to the general population. It is suggested, however, that geriatricians can make an appropriate decision on the indication and management of antithrombotic drugs for older patients. Although no studies have shown comparable findings in terms of gastrointestinal bleeding, geriatric evaluation and management has been reported to be effective to reduce serious adverse drug events.[4] A recent review on the management of antiplatelet agents[5] also recommended comprehensive strategies to reduce the risk of hemorrhagic complications. Prospective studies with a large sample size are required to confirm this issue. Nevertheless, it is certain that the use of antithrombotic

Table 1 Age, sex and medication use in case and control subjects, and unadjusted odds ratios for gastrointestinal hemorrhage

	Cases ($n = 47$)	Controls ($n = 189$)	Odds ratio (95% CI)
Age (years)	78 ± 10	77 ± 9	1.02 (0.98–1.06)
Men (women = 0, men = 1)	29 (61.7%)	120 (63.5%)	0.93 (0.48–1.79)
Antithrombotic drugs (no = 0, yes = 1)	16 (34.0)	71 (37.5)	0.86 (0.44–1.68)
Aspirin (no = 0, yes = 1)	10 (21.3)	49 (25.9)	0.77 (0.36–1.67)
Anti-ulcer drugs (no = 0, yes = 1)	18 (38.2)	45 (23.8)	0.67 (0.35–1.29)

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medi cations should be carefully determined by considering the risk/benefit balance of each patient.

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Pituitary insufficiency: A cause of hypoglycemia in an elderly diabetic patient

Dear Editor,

Hypoglycemia most likely occurs in the elderly as a result of poor glucose tolerance. The most common cause of hypoglycemia in elderly patients is antidiabetic drugs. Adrenal insufficiency, insulinoma and pituitary insufficiency are rare causes of hypoglycemia in older age.[1] Particularly in old patients, non-specific findings, such as weakness, fatigue and loss of appetite caused by pituitary insufficiency, might be attributed to aging.[2] Here, we reported an elderly patient with diabetes mellitus and hypopituitarism, presenting with refractory hypoglycemia and acute renal failure under therapy with oral antidiabetic drugs.

A 67-year-old woman was referred to geriatric clinic with symptoms of confusion, irritability, slowness of speech and movements, loss of appetite, nausea, and vomiting. A physical examination of her vital signs showed blood pressure 80/50 mmHg, pulse rate 104/min, body temperature 37.7°C and respiration 24/min. The patient was lethargic with incomplete cooperation (Karnofsky performance score of 30%). She had been taking metformin 2000 mg/day and gliclazide 30 mg/day with the diagnosis of diabetes for 2 years. In the biochemical examination, blood glucose, blood urea-nitrogen, creatinine, sodium and potassium were 32 mg/dL, 60 mg/dL, 3.2 mg/dL, 132 mmol/L and 4.9 mmol/L, respectively. After she was admitted to the geriatric clinic, her glucose infusion was given. Our initial evaluation of the clinical and laboratory parameters suggested that it could be acute renal failure as a result of dehydration and hypoglycaemia, which were the consequence of the prolonged effect of gliclazide. For this reason, oral antidiabetic drugs were discontinued, and glucose infusion was carried out. During her clinical follow up, we realized that her kidney functions had substantially increased. However, hypoglycemia persisted. Afterwards, all of the persistent hypoglycemia, hyponatremia and hypotension were evaluated, and the results were considered to be hypocortisolemia. The patient's other laboratory results, which were obtained during a hypoglycemia period, are presented in the Table 1. The basal serum cortisol (1.38 μg/dL) and adrenocorticototropic hormone levels (less than 0.3 U/L) showed strong evidence of cortisol deficiency. Due to these results, pituitary insufficiency was diagnosed. However, magnetic resonance imaging and magnetic resonance angiography did not show any structural or vascular abnormalities in the hypophysis and brain. Once prednisolone (7.5 mg/day) treatment

Table 1 Endocrinological laboratory results

Parameters		Normal range
Blood cortisol	1.38 ug/dL	6.2–19.4 ug/dL
TSH	0.055 uIU/mL	0.4–4.2 uIU/mL
Free T4	13.24 pmol/L	10.3–23.2 pmol/L
IGF-1	1.00 mg/L	1.73–5.11 mg/L
GH	<3 μg/L	
PRL	0.57 ng/mL	3–20 ng/mL
FSH	2.02 mIU/mL	25.8–134.8 mIU/mL
LH	1.36 mIU/mL	7.7–58.5 mIU/mL
Estradiol	27.96 pg/mL	5–54.7 pg/mL
C peptide	1.02 ng/mL	0.9–7.1 ng/mL
Insuline	2.83 μU/mL	3–28 μU/mL

All the laboratory results were measured between 08.00 hours and 09.00 hours, and confirmed by a second determination.
FSH, follicule stimulating hormone; GH, growth hormone; IGF1, insulin-like growth factor-1; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone; T4, thyroxine.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of polypharmacy with fall risk among geriatric outpatients

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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

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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.

Experience of falls in the past year is an established and powerful tool for assessing fall risk,[2] and was reported by the patient and/or his or her family members. Duration time of one-leg standing test, which can be carried out in a narrow limited space of the outpatient office, was measured using the leg with the eyes open, until the raised leg was put down on the floor. We examined both right and left legs once for each, and the longer of the two measurements was used for statistical analysis.[12]

Data analysis and statistical methods

Values are expressed as means ± standard deviation. In order to analyze the relationship between each fall risk index and comorbidities or drugs, variables were compared using Student's *t*-test or the χ^2-test as appropriate. The correlations between the two continuous variables were analyzed using Pearson's *r* coefficient. In multivariate analysis, logistic regression analysis was performed for history of falls and multiple regression analysis for the remaining three indices, to determine the association of fall risk with the variables. Differences between the groups of number of drugs and three indices of fall tendency were analyzed using one-factor ANOVA followed by Tukey–Kramer test. Data were analyzed using JMP version 8.0.1.

Results

The characteristics of the study subjects are shown in Table 1. Calcium channel blockers, angiotensin-II receptor blockers (ARB), statins and aspirins were prescribed in more than 20% of all the patients. Calcium channel blockers prescribed in this study were all long-acting agents, and aspirin dosage prescribed were all 100 mg. Less than 10 patients received insulin therapy, took non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics, nor antiparkinsonian drugs. Patients prescribed five drugs or more were 36.3%.

On univariate analyses, the number of drugs was the only factor which was significantly associated with history of falls in the past year (no/yes 3.2 ± 2.6/4.0 ± 3.1 drugs, $P < 0.05$). Older age, female, hypertension, osteoporosis, history of stroke, the number of comorbidities, use of ARB, aspirin, bisphosphonates, hypnotics and number of prescribed drugs were significantly associated with either one of three indices of fall risk (Table 2). Number of drugs was significantly correlated with three scores excluding the

Table 2 Univariate analysis of association between risk factor variables and three fall indices: fall-predicting score, simple screening test, one-leg standing test

		Fall risk index (points)	Simple screening test (points)	One-leg standing test (seconds)
Age		0.23***	0.23***	−0.46***
Female	No/Yes	7.0 ± 3.1/8.4 ± 4.0**	3.8 ± 3.3/4.7 ± 3.6*	19.7 ± 11.7/16.2 ± 11.7*
Hypertension	No/Yes	7.2 ± 3.6/8.4 ± 3.8*	3.7 ± 3.3/4.8 ± 3.5*	18.9 ± 11.1/16.2 ± 12.1
Osteoporosis	No/Yes	7.6 ± 3.7/8.9 ± 4.0*	4.3 ± 3.6/4.8 ± 3.1	17.9 ± 11.7/15.6 ± 11.9
History of stroke	No/Yes	7.8 ± 3.7/9.7 ± 4.1*	4.3 ± 3.4/5.6 ± 4.1	17.9 ± 11.8/8.5 ± 8.7**
Number of comorbidies		0.27***	0.17*	−0.24***
Antihypertensives	No/Yes	7.3 ± 3.6/8.5 ± 3.8*	3.7 ± 3.3/4.9 ± 3.5*	18.8 ± 11.4/15.9 ± 12.0
Angiotensin-II receptor blockers	No/Yes	7.6 ± 3.7/8.7 ± 3.8*	3.9 ± 3.4/5.2 ± 3.5**	17.6 ± 11.5/16.3 ± 12.2
Calcium channel blockers	No/Yes	7.6 ± 3.7/8.5 ± 3.7	4.1 ± 3.5/4.8 ± 3.5	18.8 ± 11.6/14.3 ± 11.6**
Aspirin	No/Yes	7.7 ± 3.8/8.9 ± 3.8*	4.1 ± 3.5/5.5 ± 3.7*	18.0 ± 11.8/13.5 ± 11.5*
Bisphosphonates	No/Yes	7.8 ± 3.8/9.9 ± 2.5*	4.3 ± 3.5/6.5 ± 2.7*	17.3 ± 11.8/14.9 ± 11.7
Hypnotics	No/Yes	7.6 ± 3.6/9.7 ± 4.1***	4.2 ± 3.6/5.2 ± 3.1	17.6 ± 11.9/15.2 ± 11.3
Number of drugs		0.30***†	0.27***†	−0.35***

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$, compared to "No" by simple Student's *t*-test. For age, number of comorbidities and number of drugs, Pearson's correlation coefficient between each indices of fall tendency are shown. †For analysis of number of drugs, a questionnaire asking "whether taking five or more drugs" were excluded for analysis. Therefore, fall risk index was analyzed by a total of 21 items, and a simple screening test by a total of 11 points. For other risk factor variables shown in the table, mean ± standard deviations are expressed. Other risk factor variables not shown in this table showed no statistically significant relationship with either one of three indices.

[Table 2 amended after online publication date September 27, 2011]

question on polypharmacy. Number of comorbidities was significantly associated with age ($r = 0.32$, $P < 0.0001$) and with the number of drugs ($r = 0.62$, $P < 0.0001$).

Next, on multivariate analyses, the questionnaire asking "whether taking five or more drugs" were excluded from the fall risk index and the simple screening test. Therefore, the fall risk index was analyzed by a total of 21 items and the simple screening test by a total of 11 points in this analysis. To evaluate the association of four fall risk indices with comorbidities and drugs, all the variables that were significantly associated in either one of four univariate analyses were entered into the model. As shown in Table 3, the number of drugs was the only factor which was significantly associated with all four indices, independent of age, sex and other variables. Because each disease variable or drug variable might have affected the number of comorbidities or the number of drugs in this analysis, we just compared the number of comorbidities and the number of drugs to exclude the double count in next analysis. As shown in Table 4, the number of drugs was significantly associated with all of the four fall risk indices independent of age, sex and the number of comorbidities, while the number of comorbidies was inversely associated with history of falls and simple screening test. As shown in Figure 1, the association of the number of drugs with

Table 3 Multivariate analysis of association between risk factor variables and four fall indices: history of falls in a year, fall risk index, simple screening test, one leg standing test

		History of fall in a year (No = 0/Yes = 1) Odds ratio (95% CI)	Fall risk index (21 items)† β	Simple screening test (11 points)† β	One-leg standing test (s) β
Age		1.00 (0.96–1.05)	0.073	0.127	−0.370***
Female	(No = 0/Yes = 1)	2.36 (1.12–5.00)*	0.199**	0.197**	−0.149*
Hypertension	(No = 0/Yes = 1)	1.87 (0.61–5.76)	0.166	0.218*	−0.110
Osteoporosis	(No = 0/Yes = 1)	0.67 (0.28–1.60)	0.093	0.027	0.023
History of stroke	(No = 0/Yes = 1)	1.43 (0.38–5.45)	0.080	0.032	−0.083
Number of comorbities		0.60 (0.38–0.95)*	−0.062	−0.237*	−0.024
Antihypertensives					
	(No = 0/Yes = 1)	0.52 (0.18–1.54)	−0.141	−0.158	0.142
Aspirin	(No = 0/Yes = 1)	1.59 (0.72–3.50)	0.053	0.046	0.002
Bisphosphonates	(No = 0/Yes = 1)	2.27 (0.73–7.07)	0.055	0.105	0.033
Hypnotics	(No = 0/Yes = 1)	0.84 (0.33–2.15)	0.094	−0.018	0.084
Number of drugs		1.24 (1.07–1.45)*	0.247**	0.335***	−0.250**

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$. Logistic regression analysis was performed for history of fall in a year, and multiple regression analysis for the remaining three. The risk factor variables used in these multivariate analyses were those associated in either of the four univariate analysis significantly. †The questionnaire asking "whether taking five or more drugs" were excluded from the scores in this analysis. Therefore, fall risk index were analyzed by a total of 21 items and simple screening test by a total of 11 points. CI, confidence interval; β, standardized regression coefficient.
[Table 3 amended after online publication date September 27, 2011]

Table 4 Multivariate analysis of association between number of comorbidities and drugs with four fall indices: history of falls in a year, fall risk index, simple screening test, one-leg standing test

	History of fall in a year (No = 0/Yes = 1) Odds ratio (95% CI)	Fall-risk index (21 items)† β	Simple screening test (11 points)† β	One-leg standing test (s) β
Age	1.00 (0.96–1.05)	0.101	0.115	−0.376***
Female (No = 0/Yes = 1)	1.73 (0.90–3.34)	0.207**	0.191**	−0.110
Number of comorbidities	0.63 (0.45–0.89)*	0.073	−0.137	−0.034
Number of drugs	1.23 (1.08–1.41)*	0.223*	0.316***	−0.233**

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$. Logistic regression analysis was performed for history of fall in a year, and multiple regression analysis for the remaining three. †The questionnaire asking "whether taking five or more drugs" were excluded from the scores in this analysis. Therefore, fall risk index was analyzed by a total of 21 items and simple screening test by a total of 11 points. CI, confidence interval; β, standardized regression coefficient.

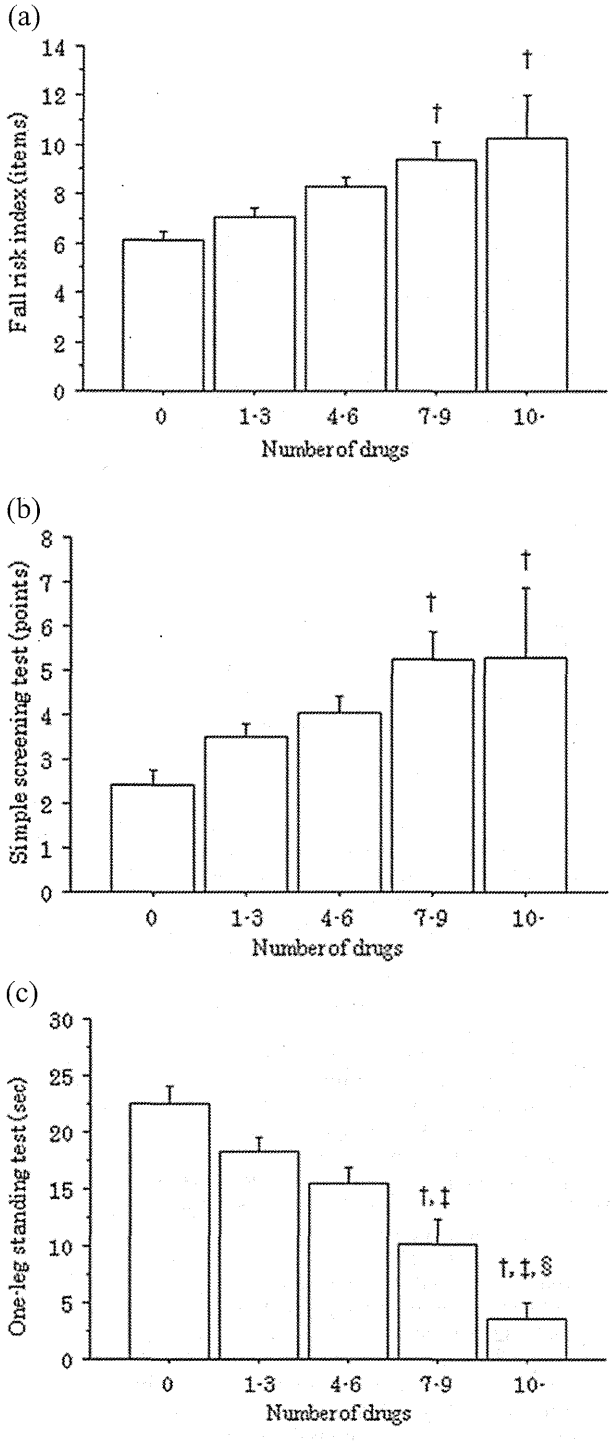

Figure 1 Averages of fall risk according to the number of drugs. (a) Fall risk index excluding the questionnaire concerning polypharmacy. (b) Simple screening test excluding the questionnaire concerning polypharmacy. (c) Duration time of one-leg standing test. The differences between the number of the drugs were compared through ANOVA, $P < 0.0001$ for (a), $P < 0.005$ for (b), $P < 0.0001$ for (c). For post-hoc analysis, $^{\dagger}P < 0.05$ vs 0 drug; $^{\ddagger}P < 0.05$ vs 1–3 drugs; $^{\S}P < 0.05$ vs 4–6 drugs. Values are expressed as mean ± standard error.

fall predicting score, simple screening test and duration time of one-leg standing test was stepwise.

Discussion

Epidemiological studies have assessed the risk of falls in community-dwelling people, but not in geriatric outpatients, who are likely to fall and need special consideration for the treatment of their illness. This cross-sectional study investigated the association between comorbidities, medications and fall risks in Japanese elderly outpatients and found that all four indices were significantly associated with the number of drugs. Because polypharmacy is frequently seen in patients with multiple comorbidities, this study compared the impact of the number of drugs with that of the number of comorbidities on fall risk, and found the significance of polypharmacy as fall risk in elderly outpatients.

In the present study, the number of comorbidities was inversely associated with the history of fall in the past year and with an 11-point simple screening test in the multivariate analysis. The reason is unclear; however, there are some speculations about this. None of the patients with four or more comorbidities ($n = 19$, 79.4 ± 5.2 years old) had history of fall in the past year. This accounts for the lower points of the simple screening test in these patients, because the history of fall consists of 5 points out of a total of 11 points in the simple screening test. So the question is why they had lower frequency of falling experiences, although they are at higher risk of falls according to fall risk index and one-leg standing test (9.6 ± 3.8 items and 8.6 ± 9.4 s, respectively). These patients may take care not to fall in their daily lives because of their consciousness of fall risk or frailty, or maybe due to elevated vigilance of caregivers and their constant physical assistances. They might have simply forgotten their fall experiences due to subclinical cognitive impairment, although demented patients were not included in this study. It is also possible that the patients who had more comorbidities and had fallen did not meet our inclusion criteria because of their recent injurious falls or their severe conditions.

Several medications and comorbidities have been reported as risks of fall.[6,7,13–19] Among these, diabetes,[9,10] imsonia,[13] hypnotics[13–15] and antihypertensive use[8] were not significantly associated with fall risk in our study. Only 20 patients (40.8% of diabetic patients) were prescribed hypoglycemic agents such as sulfonylurea ($n = 17$) or insulin ($n = 3$) in this study. Because hypoglycemia is considered to be the main cause of accidental falls in diabetic patients, relatively less prescription of hypoglycemic agents might have affected our result. The patients who were prescribed hypnotics tended to be at higher risk of falls in univariate analysis, which did show statistical significance. Also, antihypertensives such as diuretics are reported to increase the fall risk.[8] No

association between these drugs and fall risk in our study might be due to the small sample size. Other drugs such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonians[19] might increase fall risk; however, very few patients used these drugs in this study.

There are some other limitations. First, the causal relationship of the associations observed in this study is unknown because of the cross-sectional design. Polypharmacy has been regarded as a risk in several aspects in elderly patients. Previous studies have shown that adverse drug events were seen more frequently in the polypharmacy patients during their stay in the geriatric inpatient ward,[20] and polypharmacy was one of the important predictors for postdischarge mortality in elderly patients after emergent hospitalization.[21] Because patients with multiple diseases and in severer conditions are likely to take more medications, we used the number of comorbidities in analysis as fall risk variables. However, it is still unclear whether polypharmacy is a risk of falls independent of severity of each comorbidity. Interventional studies to reduce the number of drugs are needed to clarify the causal relationship between polypharmacy and fall risk. Second, this study did not evaluate the fall itself. The validity of four indices used in this study is well established as fall risk markers. However, prospective studies which evaluate the incidence of fall should be carried out in the future. Third, although the included subjects were receiving the same prescriptions for more than 1 month, the exact duration of each drug use or polypharmacy was not assessed in this study. Consequently, the long-term adverse effects over months or years seen in elderly patients should be more precisely investigated.

In summary, this study demonstrated that geriatric outpatients with polypharmacy were at higher risk of falls, consistent with the previous studies conducted in community-dwelling elderly. Our finding may add new information on pharmacotherapy in elderly patients with chronic diseases. Prospective studies and intervention studies examining the effect of drug reduction are needed in the future.

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Appendix I. 22 items of fall-predicting score (questionnaire)

Q1. Have you fallen during the last 12 months?	Yes, 1; No, 0.
Q2. Have you tripped during the last 12 months?	Yes, 1; No, 0.
Q3. Can you climb stairs without help?	Yes, 0; No, 1.
Q4. Do you feel your walking speed has declined recently?	Yes, 1; No, 0.
Q5. Can you cross a road within the green signal interval?	Yes, 0; No, 1.
Q6. Can you walk 1 km without stopping?	Yes, 0; No, 1.
Q7. Can you stand on one foot for about five seconds?	Yes, 0; No, 1.
Q8. Do you use a stick when you walk?	Yes, 1; No, 0.
Q9. Can you squeeze a towel tightly?	Yes, 0; No, 1.
Q10. Do you feel dizzy at times?	Yes, 1; No, 0.
Q11. Is your back bent?	Yes, 1; No, 0.
Q12. Do you have knee pain?	Yes, 1; No, 0.
Q13. Do you have a problem with your vision?	Yes, 1; No, 0.
Q14. Do you have a hearing problem?	Yes, 1; No, 0.
Q15. Do you think you are forgetful?	Yes, 1; No, 0.
Q16. Do you feel anxious about falling when you walk?	Yes, 1; No, 0.
Q17. Do you take five or more prescribed medicines?	Yes, 1; No, 0.
Q18. Do you feel unsafe because your home is dark?	Yes, 1; No, 0.
Q19. Are there any obstacles in your house?	Yes, 1; No, 0.
Q20. Is there any difference in level within your home?	Yes, 1; No, 0.
Q21. Do you have to use stairs in daily living?	Yes, 1; No, 0.
Q22. Do you have to walk on a steep slope around your house?	Yes, 1; No, 0.

Appendix II. Simple screening test for risk of falls

Q1. Have you fallen during the last 12 months?	Yes, 5 points; No, 0.
Q2. Do you feel your walking speed has declined recently?	Yes, 2 points; No, 0.
Q3. Do you use a cane when you walk?	Yes, 2 points; No, 0.
Q4. Is your back bent?	Yes, 2 points; No, 0.
Q5. Do you take five or more prescribed medicines?	Yes, 2 points; No, 0.

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ORIGINAL ARTICLE

Plasma sex hormone levels and mortality in disabled older men and women

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Aim: To investigate the relationship between circulating sex hormone levels and subsequent mortality in disabled elderly.

Methods: This prospective observational study was comprised of 214 elderly subjects aged 70–96 years (117 men and 97 women; mean ± standard deviation age, 83 ± 7 years), receiving services at long-term care facilities in Nagano, Japan. All-cause mortality by baseline plasma sex hormone levels was measured.

Results: After excluding deaths during the first 6 months, 27 deaths in men and 28 deaths in women occurred during a mean follow up of 32 months and 45 months (up to 52 months), respectively. Mortality rates differed significantly between high and low testosterone tertiles in men, but did not differ significantly between middle and low tertiles. Compared with subjects in the middle and high tertiles, men with testosterone levels in the low tertile (<300 ng/dL) were more likely to die, independent of age, nutritional status, functional status and chronic disease (hazard ratio [HR] = 3.27, 95% confidence interval [CI] = 1.24–12.91). In contrast, the low dehydroepiandrosterone sulfate (DHEA-S) tertile was associated with higher mortality risk in women (multivariate adjusted HR = 4.42, 95% CI = 1.51–12.90). Exclusion of deaths during the first year and cancer deaths had minimal effects on these results. DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Conclusion: Low testosterone in men and low DHEA-S in women receiving care at facilities are associated with increased mortality risk, independent of other risk factors and pre-existing health conditions. **Geriatr Gerontol Int 2010; 10: ••–••.**

Keywords: dehydroepiandrosterone, disabled elderly, mortality risk, testosterone.

Introduction

Japan has the longest life expectancy at birth in the world for both men and women, although women live 8 years longer than men on average.[1,2] One explanation for this phenomenon is that estradiol production during the premenopausal years partially protects women from cardiovascular disease (CVD). In contrast, there has been a suspicion that testosterone itself is harmful; however, recent studies support the hypothesis that testosterone may be beneficial to survival in aging men.[3–8]

It is well established that endogenous androgens decline with advancing age in men.[9] Because testosterone has important physiological effects on muscle, bone, brain, erythropoietin and the vascular system, decreased testosterone levels could contribute to age-associated symptoms and diseases in older men, such as decreased muscle mass and strength,[10] impaired physical performance,[11,12] osteoporosis[13] and fractures,[12,14]

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depressed mood,[15] cognitive impairment,[16,17] anemia[18,19]and frailty.[20] In our previous study in which older persons receiving day-care services or admitted to a facility were investigated, higher plasma testosterone levels were associated with better activities of daily living (ADL), cognitive function and vitality in men.[21] On the other hand, several epidemiological studies have demonstrated that a decline in testosterone level was associated with mortality risk in community-dwelling middle-aged or older men.[3–8] In cause-specific analyses, some studies have shown that a low testosterone level was associated with an increased risk of death due to CVD.[4,5] However, the above-mentioned studies were performed in community samples of Caucasian men, and this issue remains to be clarified in frail or disabled older men.

The majority of dehydroepiandrosterone (DHEA), an endogenous steroid precursor to testosterone and estrogen, exists as the sulfated form (DHEA-S) in the circulation, and DHEA and DHEA-S are the most abundant adrenal sex steroid hormones, with concentrations reported to be more than 100-fold higher than those of testosterone and estradiol,[22] suggesting an important physiological role of DHEA(-S). Their circulating levels also peak in young adults and decline with age in both men and women. Although the role of androgens in older women's health is not fully understood, postmenopausal women with intact ovaries continue to produce androgens, DHEA and testosterone, while their production of estradiol is minimal.[23] In our previous study,[21] in older women, higher DHEA and DHEA-S levels were related to better ADL, while estradiol and testosterone levels showed no relations. Other reports have shown a correlation between DHEA level and cognitive function,[24] depression,[25] osteoporosis[26] and frailty in older women.[27] Several studies that examined the association between DHEA-S and mortality in women have shown mixed results,[28–32] and mostly found no relation; however, both low and high levels of DHEA-S at baseline[28] and some trajectory patterns such as a steep decline or extreme variability[32] have been reported to correlate with increased mortality.

These lines of evidence suggest that endogenous androgens, including testosterone and DHEA(-S), may play a role in physical and mental function as well as longevity in older individuals. We hypothesized that low plasma androgen levels could be a mortality risk factor even in elderly with disability who are receiving facility services.

Methods

Study population

In this longitudinal observational study, 218 consecutive persons aged 70 years or older (121 men aged 70–96 years and 97 women aged 70–95 years; mean ± standard deviation [SD] age, 83 ± 6 and 83 ± 5 years, respectively) who attended health service facilities for the elderly (facilities that provide nursing care and rehabilitation services to elderly people with disability, *Mahoroba-no-Sato*) located in Nagano Prefecture, Japan were enrolled. The participants were in a chronic stable condition and receiving services under Long-term Care Insurance, which is provided by the Japanese Government, either under admission or as day care. The principal exclusion criteria were malnutrition (serum albumin <3.5 mg/dL or body mass index [BMI] <16 kg/m^2), extremely low ADL status (Barthel Index[33] <50), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment), severe anemia (blood hemoglobin <10.0 g/dL) and overt endocrine disease because these conditions may affect both plasma sex hormone levels and mortality. Deaths that occurred during the first 6 months of follow up (four men and no women) were also excluded to minimize the influence of comorbidity on both sex hormone levels and mortality; therefore, the remaining 214 persons were analyzed in this study. The institutional review board of *Mahoroba-no-Sato* approved the study protocol, and all participants and/or their family members gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). Testosterone and estradiol were assayed using chemiluminescence immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. DHEA-S was assayed using a sensitive radioimmunoassay with a minimum detection limit of 2.0 μg/dL (0.05 μmol/L). The intra-assay coefficients of variation for these measurements were less than 5%.

Functional and anthropometric measurements

Trained nurses and physical therapists visited the participants at the health facilities and performed comprehensive geriatric assessments. Basic ADL was assessed by Barthel Index,[33] cognitive function by Hasegawa Dementia Scale – Revised (HDS-R, 30-point scale),[34] mood by the Geriatric Depression Scale (GDS, 15 items),[35] and ADL-related vitality by Vitality Index (10-point scale).[36] BMI was calculated

as weight in kilograms divided by the square of height in meters.

Comorbidity

Diseases were ascertained by experienced physicians according to pre-established criteria that combine information from self-reported physician diagnoses, medical records, current medication, clinical examinations and blood tests. Diseases included in the current analysis were hypertension, heart disease (including any of angina pectoris, myocardial infarction, congestive heart failure and arrhythmia), stroke, diabetes mellitus, osteoarthropathy (arthritis, rheumatism, osteoporosis and history of fractures), lung disease (including bronchial asthma and chronic obstructive pulmonary disease) and other chronic diseases (chronic kidney disease, gastrointestinal disease, Parkinson's disease and psychological disorders). We also obtained data on anti-androgenic treatment and intake of glucocorticoids, opiates and hormone supplements that could affect plasma hormone levels, but no subject was taking any of these.

Follow up

The subjects were followed up in 2002–2009, for a period of up to 52 months (mean ± SD, 32 ± 13 [34] months in men and 45 ± 11 [49] months in women). Time and causes of death of deceased persons were ascertained using medical records and death certificates. All deaths were registered with International Classification of Diseases, 10th version (ICD-10) codes,[37] based on the information from death certificates. We categorized deaths into the following four specific causes: (i) diseases of the circulatory system (I00–I99) including heart disease and cerebrovascular disease; (ii) diseases of the respiratory system (J00-J99); (iii) neoplasms (C00-D48); and (iv) other causes. Subjects who were alive were confirmed by checking appointment records of the facilities. Survival of 16 subjects whose records were not available was ascertained by the phone interview of each subject. Causes of death were determined for all the subjects without any missing cases.

Statistical analysis

Differences between testosterone tertiles in men and between DHEA-S tertiles in women were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. Survival was analyzed using Kaplan–Meier plots and log–rank tests. Hazard ratios (HR) for mortality were analyzed using Cox proportional hazards regression. Significance tests were two-sided, with an α-level of 0.05. Data were analyzed using SPSS statistical software.

Results

Characteristics of study subjects

Over the follow-up period, 27 men and 28 women died, yielding a mortality rate of 86.5/1000 person-years at risk in men; and 69.9/1000 person-years at risk in women. Of those, 13 deaths were due to diseases of the circulatory system (eight to ischemic and other heart disease and five to cerebrovascular disease), 10 to diseases of the respiratory system and four to cancer in men; while 14 deaths were due to diseases of the circulatory system (nine to ischemic and other forms of heart disease and four to cerebrovascular disease), eight to diseases of the respiratory system, five to cancer and two to other causes in women. Men who died were significantly older, had lower serum albumin and cholesterol, lower ADL and cognitive status, higher prevalence of heart disease, and lower testosterone level than survivors; whereas in women, subjects who died were older, had lower hemoglobin, higher prevalence of heart disease and lower plasma DHEA-S level than survivors (data not shown).

Table 1 shows the baseline characteristics of the male subjects by tertile of plasma testosterone. A significant difference was observed in serum albumin and hemoglobin levels, ADL and cognitive status among tertiles of testosterone in men. Table 2 shows the baseline characteristics of the female subjects by tertile of plasma DHEA-S. A significant difference was found in age and ADL status among DHEA-S tertiles in women, while other variables did not differ between the tertile groups.

Mortality and plasma sex hormone levels in men

As shown in Figure 1(a), Kaplan–Meier survival analysis by tertile of plasma testosterone level revealed that testosterone level was associated with mortality in men. After adjusting for age, Cox proportional hazards models showed that there was an inverse relation between testosterone level and mortality. Mortality rate differed significantly between the high and low testosterone tertiles, but not significantly between the middle and low tertiles: tertile 3 (high), reference; tertile 2 (middle), HR = 2.51 (95% confidence interval [CI] = 0.66–9.50); and tertile 1 (low), HR = 6.63 (95% CI = 1.92–23.21). Accordingly, we investigated the increased mortality in tertile 1 versus tertiles 2–3 (Table 3). Compared with subjects within tertiles 2–3,

Table 1 Association between potential confounding variables and testosterone tertiles in men

Characteristic	Testosterone tertiles T1 <10.4 nmol/L (<300 ng/dL), *n* = 39	T2 10.4–16.3 nmol/L (300–470 ng/dL), *n* = 40	T3 >16.3 nmol/L (>470 ng/dL), *n* = 38	*P*-value
Age, years	83 ± 7	83 ± 6	81 ± 6	0.11
Nutritional parameters				
Body mass index, kg/m^2	21.3 ± 3.4	22.8 ± 3.8	21.7 ± 3.0	0.21
Hemoglobin, g/dL	12.7 ± 1.9	13.8 ± 1.3	14.0 ± 1.7	<0.01
Albumin, g/dL	4.0 ± 0.3	4.1 ± 0.2	4.2 ± 0.3	<0.01
Total cholesterol, mg/dL	173 ± 38	195 ± 36	176 ± 28	0.05
Prevalent diseases, *n* (%)				
Hypertension	17 (44)	16 (40)	12 (32)	0.53
Heart disease	10 (26)	5 (13)	7 (18)	0.32
Stroke	12 (31)	15 (38)	8 (21)	0.34
Diabetes mellitus	8 (21)	5 (13)	8 (21)	0.31
Osteoarthropathy	8 (21)	9 (23)	7 (18)	0.94
Lung disease	2 (5)	3 (8)	3 (8)	0.52
Other chronic diseases	17 (44)	19 (48)	18 (47)	0.95
Functional parameters				
Barthel Index	79 ± 12	82 ± 11	87 ± 13	0.04
HDS-R	18 ± 7	19 ± 6	22 ± 5	0.02
Vitality Index	9.2 ± 1.1	9.3 ± 0.9	9.5 ± 0.9	0.46
GDS	5.0 ± 3.1	5.6 ± 3.7	5.6 ± 2.9	0.66
Sex hormone levels				
Testosterone, nmol/L	7.6 ± 2.5	13.3 ± 1.6	20.9 ± 3.9	<0.01
(ng/dL)	(219 ± 73)	(382 ± 43)	(602 ± 112)	
DHEA-S, μmol/L	1.7 ± 1.1	1.8 ± 1.6	1.7 ± 1.2	0.94
(μg/dL)	(64 ± 42)	(69 ± 57)	(63 ± 45)	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

a testosterone level within tertile 1 was associated with approximately fourfold higher mortality risk. Adjustment for age, nutritional parameters (BMI, albumin, hemoglobin, total cholesterol) and functional parameters (Barthel Index, HDS-R, Vitality Index, GDS), and prevalent diseases showed no major influence on the result. In order to examine how follow-up time and cancer impacted on the results, assuming that the subjects may have had subclinical cancer or a fatal illness at baseline, we performed further analyses excluding deaths that occurred in the first 12 months ($n = 9$) and deaths from cancer ($n = 4$). However, the significant associations remained after these exclusions (Table 3). On the other hand, DHEA-S level was not associated with mortality when DHEA-S was entered as tertiles (data not shown).

Although the statistical power was not strong enough, we studied the risk for cause-specific mortality by tertiles of testosterone level in men. Neither deaths from diseases of the circulatory system nor those from non-circulatory causes showed a significant association with testosterone tertiles (tertile 1 vs tertile 2–3, HR = 3.18, 95% CI = 1.87–11.6, $P = 0.17$; HR = 3.46, 95% CI = 0.29–7.29, $P = 0.64$, respectively).

Mortality and plasma sex hormone levels in women

As shown in Figure 1(b), a low DHEA-S level was associated with higher mortality by Kaplan–Meier survival analysis. Age-adjusted Cox proportional hazards models revealed that the association was not significant when each tertile of DHEA-S was entered as a continuous variable; however, a significant association was observed when tertile 1 was compared with tertiles 2–3 (Table 3). The association remained significant after excluding deaths that occurred in the first 12 months ($n = 2$) and deaths from cancer ($n = 5$). Moreover, further adjustment had no major influence on the result. In women, testosterone and estradiol levels were not associated with mortality when they were entered as tertiles (data not shown).

In cause-specific mortality analysis, compared with tertiles 2–3, the low tertile of DHEA-S level was associated with higher risk of death from diseases of the