倒リスクの報告がみられた[11].

考察と結論

BPSDに対する抗精神病薬の使用は，ある程度の効果は認められるが，その一方で死亡リスクの上昇，脳血管障害のリスクの上昇などが認められるため，非薬物療法や環境調整をまず実施し，その後効果と安全性のバランスを慎重に吟味した上で，使用を検討するべきであろう．同様に不眠症に対する睡眠薬の使用も，認知機能や運動機能低下のリスクがあるため，まず睡眠衛生指導を積極的に行うべきと考えられる．認知行動療法的なアプローチの有用性も報告されている[12]．また，より高齢のうつ病に対して，抗うつ薬の効果がないとする報告もみられたことは，高齢者のうつ病が心理，社会的要因の影響も大きく受けていることや，その点に対する対応が重要なことを示唆している．今回の結果の範囲ではSSRIの効果は，SNRIや三環系抗うつ薬とほぼ同等と考えられる．一般に安全性が比較的高いと考えられているSSRIでも，高齢者に対しては転倒のリスクが報告されていることから，安全性についてさらなる注意が求められる．

まとめ

今回は2005年以降の論文について検討し，それ以前の研究については対象としていない．現在，文献の検索範囲を広げて追加検索を実施している．

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Original Study

Low Testosterone Levels, Depressive Symptoms, and Falls in Older Men: A Cross-Sectional Study

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depression
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A B S T R A C T

Objectives: While several studies have cited a potential association between testosterone deficiency and risk of falls among community-dwelling older men, evidence for such an association is conflicting. Depressive symptoms, which occasionally accompany testosterone deficiency but which are often neglected as associated symptoms, may actually provoke falls independent of or jointly with testosterone deficiency. We examined the association between testosterone levels, depressive symptoms, and falls, and assessed the joint effect of testosterone levels and depressive symptoms on falls among older men.
Design, Setting, and Participants: Data for this cross-sectional study were obtained from 869 men aged over 60 years who participated in health check-ups conducted in 2010 from 2 Japanese municipalities. Salivary testosterone (sT) levels were measured using an enzyme-linked immunosorbent assay, and depressive symptoms were assessed via the short form of the Center for Epidemiologic Studies Depression Scale.
Main outcome measures: Self-reported "any fall" over the 1-month period.
Results: Among the total of 482 participants analyzed (median age, 70 years), 10.8% reported any fall. On comparison between 90th percentile sT levels and lower levels, our logistic regression model with restricted cubic splines showed that lower sT levels were associated with an increased likelihood of suffering any fall after adjustment for sociodemographic characteristics, comorbidities, and mobility function. For example, 5th percentile sT was associated with any fall [adjusted odds ratio (OR), 4.23; 95% confidence interval (CI), 1.66–10.8]. Depressive symptoms were also strongly associated with any fall [adjusted OR, 3.49 (95% CI, 1.52–8.04)]. We noted no apparent interaction of sT and depressive symptoms with falls ($P = .079$), suggesting that the joint effect of testosterone deficiency and depressive symptoms on falls was multiplicative. Indeed, compared with a combination of 90th percentile sT values and no depressive symptoms, adjusted OR for any fall in a combination involving 5th percentile sT and depressive symptoms was 14.8-fold (95% CI, 3.76–58.0).
Conclusions: Our findings indicated that both relatively low testosterone levels and presence of depressive symptoms were independently associated with falls among older men. Causality of these associations should be confirmed in future prospective studies.

Falls are a serious public health problem, with one-third of community-dwelling individuals aged over 65 years falling at least once annually[1] and with 5% to 10% of falls resulting in fracture, head injury, or other serious injuries.[2] While falls in older individuals are multifactorial, age-related decline in lower extremity strength or

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mobility function are recognized as important contributors.[2–5] Separately, age-related decline in testosterone levels in men is a growing concern, with approximately 30% of men aged 40–79 years showing testosterone deficiency.[6] However, while previous studies have suggested that low testosterone levels are associated with reduced extremity strength or mobility function in older men,[7,8] relatively few have examined the association between low testosterone levels and falls, with conflicting results despite the ostensibly plausible biological connections.

One concern with these previous studies examining the relationship between testosterone deficiency and falls is their lack of consideration for presence of depressive symptoms.[9–11] Testosterone-deficient individuals are likely to have concurrent depressive symptoms,[12] and depressive symptoms are also associated with falls.[4] One study found no association between testosterone levels and incident falls after adjustment for confounders including depressive symptoms,[13] suggesting the potential importance of examining the effects of testosterone deficiency on falls independent of depressive symptoms. In addition, if both testosterone deficiency and depressive symptoms are proven to be associated with falls, whether or not men with *both* testosterone deficiency and depressive symptoms are more likely to suffer falls than those with either condition alone would also be of clinical relevance, as these individuals are likely to be seen by physicians specialized in treating testosterone deficiency.[14,15]

Here, to examine whether or not testosterone deficiency and depressive symptoms are independently associated with falls in community-dwelling older men, we analyzed data from the Locomotive Syndrome and Health Outcome in Aizu Cohort Study (LOHAS). We further evaluated how the strength of the association between the composite of testosterone deficiency and depressive symptoms and falls is larger or smaller than the product of the strength of the association between testosterone deficiency and falls and that between depressive symptoms and falls.

Methods

Our cross-sectional study was approved by the Research Ethics Committee of Fukushima Medical University School of Medicine. The LOHAS is a population-based study conducted starting in 2008 involving residents aged 40–80 years who participated in annual health check-ups among 2 communities (Tadami and Minamiaizu Towns) in Fukushima Prefecture, Japan. Eligibility criteria for this study were "aged over 60 years" and "participated in the health check-up conducted in 2010." No exclusion criteria were set. All participants provided written informed consent. Details of the design of the LOHAS have been reported previously.[16]

Measurement of Salivary Testosterone

Salivary concentration of testosterone (sT) was the main exposure, measured using an enzyme-linked immunosorbent assay (ELISA) on the RE52631 system (IBL International GmbH, Hamburg, Germany) and expressed in pg/mL (to convert to picomoles per liter, multiply by 3.47). sT reflects the level of free testosterone in plasma. Saliva was collected in the morning, at least 30 minutes after breakfast. Participants rinsed their mouth gently with water and were asked to avoid brushing their teeth. All participants collected whole saliva by directly spitting into polypropylene tubes through a polypropylene straw-tube. If a participant had little saliva, he was instructed to chew gum prepared specially for saliva collection. The supernatants of saliva obtained after centrifugation (3000 × g, 10 minutes) were kept at −80°C for further analysis. sT was measured in the laboratory of Teikyo University (Tokyo, Japan). For men aged 20–40 years, median sT is 139.4 pg/mL (10th to 90th percentile, 43.8–288.0 pg/mL). The intra- and interassay coefficients of variance were 3.9%–8.8% and 6.7%–8.0%, respectively. Slight cross-reactions with other natural steroids in the human body and their profiles were as follows: dihydrotestosterone, 2.5%; androstenedione, 0.85%; and others, <0.1%.[17]

Depressive Symptoms

Depressive symptoms were considered as secondary exposures in light of their usefulness in predicting fall risk according to the literature and their potentially close association with testosterone deficiency.[4,12] Depressive symptoms were assessed using the 10-item version of the Center for Epidemiological Studies Depression Screening Index (CES-D). The cutoff score for depressive symptoms was set as a score of 10 or greater, as was recommended in the literature.[18] Although data on physician-diagnosed depression was unavailable in the LOHAS study, we assumed its use would considerably underestimate the true proportion of depression, as previous studies have shown that depression is underdiagnosed more often by Japanese physicians than those in other countries due to stigma related to psychiatric disorders within Japanese society.[19,20]

Clinical Outcomes

We examined "any fall over a 1-month period" as the clinical outcome based on participants' answers to the question, "Over the past year, have you fallen down?" to establish fall history. Participants who responded, "Yes," were then asked the follow-up question, "How many times have you fallen down over the past month?" with responses of "zero," "once," "twice," or "three or more times" allowed. Those who reported at least "once" were considered to have had "any fall" over the previous month. Regarding our decision to examine falls over the previous month instead of the previous year, we believed that reverse-causality would be more unavoidable if we were to use fall over the past year rather than the past month in investigating relationship with present sT level, and a systematic review has suggested that recalling fall experience at a 1-year interval might underestimate true fall incidence compared to recalling incidence at a 1-month interval.[21]

Measurement of Potential Confounding Variables

Potential confounding variables examined in the present study were sociodemographic characteristics including age, exercise habit, and living alone, as well as the presence of cerebrovascular disease and the presence of incontinence, all obtained via self-reported questionnaire; body mass index and blood pressure, as measured by local nurse practitioners; hypertension, defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or by individuals reporting attending a physician for treatment; diabetes, defined as having glycosylated hemoglobin values ≥6.1%, as described by the Japanese Diabetes Society [equivalent to ≥6.5% described in National Glycohemoglobin Standardization Program values[22]] or by individuals reporting attending a physician for treatment; and timed up and go (TUG) test. Individuals were considered to engage in exercise if they answered "yes" to the question concerning whether or not they had participated in moderate physical activity (making the individual breathe somewhat harder than normal and including situations such as carrying light loads, bicycling at a regular pace, or doubles tennis) in the previous 7 days. Individuals were considered to have incontinence if they answered "once a week or more" to the question of whether or not they leaked urine because they could not defer the sudden urge to urinate. The TUG test, in which individuals are timed when rising from a chair, walking 3 m, and turning to return to sit on the chair, is considered to be a reflection of function in

gait, balance, and mobility[23] with a greater score indicating more mobility problems.

Statistical Analysis

Participants with complete data were entered into primary analyses. Statistical analyses were conducted using Stata v. 11.0 (StataCorp, College Station, TX). sT, depressive symptoms, sociodemographic characteristics, comorbidities, TUG, and any fall over the previous month were described. Box plots for sT stratified by age categories were also created. Effect measures in the present study were odds ratios (OR)s of sT and depressive symptoms for likelihood of having any fall in the past month estimated using logistic regression models. To estimate adjusted ORs, the potential confounding variables described above were simultaneously forced into the models along with sT and depressive symptoms.

Given that the association of sT (as continuous variables) and falls might have been nonlinear, as such nonlinear relationships are well-established for several hormonal systems in the endocrinology literature, separate models were constructed to assess the shape of the association between sT and falls, where sT was included as (1) a linear variable, (2) a log-transformed variable, (3) a transformation using restricted cubic splines with 3 knots, and (4) 5 quintiles. To assess the fitness of these models, the Akaike information criterion, which is a likelihood-based measure that adds a penalty for model complexity, were reported.[24]

While nonlinear models were superior to the linear model in terms of the Akaike information criterion, the 5-quintile model and the restricted cubic spline model were similar to one another (Supplementary Table 1). We therefore chose the restricted cubic spline model for primary analysis, as this model provided a good fit and was the most parsimonious, and we based all further testing on it. In this model, the 90th percentile of sT was chosen as a reference, as it corresponds to the median of the highest quintile. The potential effect modification of depressive symptoms on the association between sT and any fall over the previous month was examined by likelihood ratio test, adding interaction pair (the product terms of sT with depressive symptoms) to the logistic regression models.

Sensitivity Analysis

In addition to the above, we also conducted 3 sensitivity analyses. First, the association between sT and fall was reported, with 5 quintiles of sT included, citing the top category of the quintiles as reference. Second, the association between sT and falls was examined including 280 participants with missing covariate values. In this analysis, restricted cubic splines with 3 knots were used with adjustment for covariates via the missing indicator method. Third, CES-D was used as exposure instead of depressive symptoms, and the association between CES-D score and fall was examined. *P* value of <.05 was considered statistically significant.

Results

Of the 869 men who underwent the health check exam (Figure 1), 58 and 13 participants were missing data for sT and any falls, respectively. After exclusion of 36 participants with poor-quality saliva specimens (because of inadequate amount obtained or suspected blood contamination), 762 (87.7%) remained with both sT and outcome variables. After exclusion of a further 280 participants with at least 1 confounding variable missing, the remaining 482 participants were ultimately entered into the primary analyses.

Baseline characteristics are presented in Table 1. Median age in the present study was 70 years (10th to 90th percentile, 63–78 years).

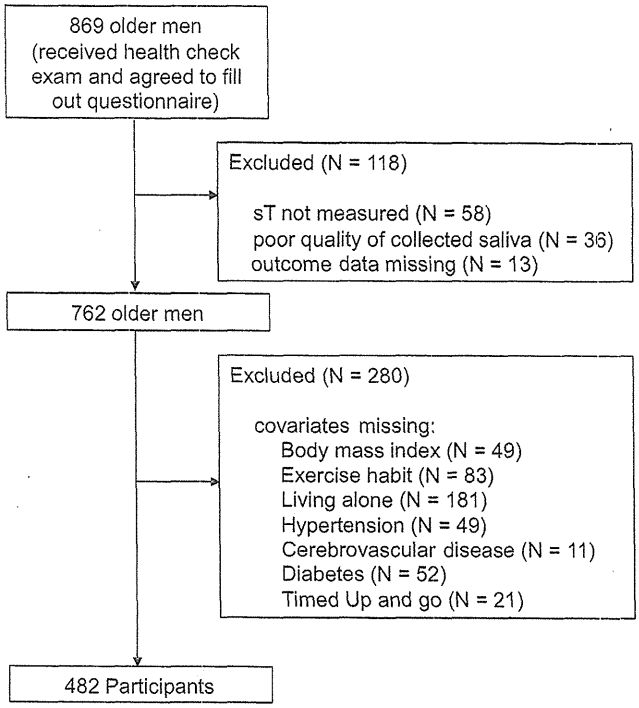

Fig. 1. Flow chart of study participants. Sum of number of participants with missing values for each covariate exceeds 280 because 90 participants had missing values for 2 or more covariates. sT, salivary testosterone.

The prevalence of hypertension and diabetes were 69.3% and 14.5%, respectively. Median sT was 58.7 pg/mL (10th to 90th percentile, 26.3–146 pg/mL). Box plots for sT showed that median sT was highest among those aged 60–64 years and lowest among those aged over 80 years (Figure 2). The prevalence of depressive symptoms was 11.6%. The prevalence of any fall over the previous month was 10.8%.

Sociodemographic characteristics were similar between participants with and without missing confounding variables (Supplementary Table 2) except for exercise habit. As a group, their sT, TUG value, proportion with depressive symptoms, and proportions of any fall over the 1-month period examined were similar. As a group, baseline characteristics among participants in the primary

Table 1
Baseline Characteristics of the Analysis Population

	Total (n = 482)	No Falls Over the Previous Month (n = 435)	Any Fall Over the Previous Month (n = 47)
Age, y			
Median	70	70	71
10th to 90th percentile	63–78	63–78	63–79
Body mass index, kg/m^2			
Median	23.8	23.8	24.4
10th to 90th percentile	20.2–27.3	20.2–27.4	21.1–26.6
Exercise habit, n (%)	264 (54.8)	235 (54.0)	29 (61.7)
Living alone, n (%)	61 (12.7)	53 (12.2)	8 (17.0)
Incontinence, n (%)	38 (7.9)	35 (8.1)	3 (6.4)
Hypertension, n (%)	334 (69.3)	302 (69.4)	32 (68.1)
Cerebrovascular disease, n (%)	28 (5.8)	21 (4.8)	7 (14.9)
Diabetes, n (%)	70 (14.5)	64 (14.5)	7 (14.9)
Timed Up and Go, s			
Median	7.1	7.1	8.0
10th to 90th percentile	5.4–9.5	5.3–9.4	5.7–10.5
Depressive symptoms, n (%)	56 (11.6)	45 (10.3)	11 (23.4)
Salivary testosterone, pg/mL			
Median	58.7	61.0	47.8
10th to 90th percentile	26.3–146	26.3–147	25.8–133

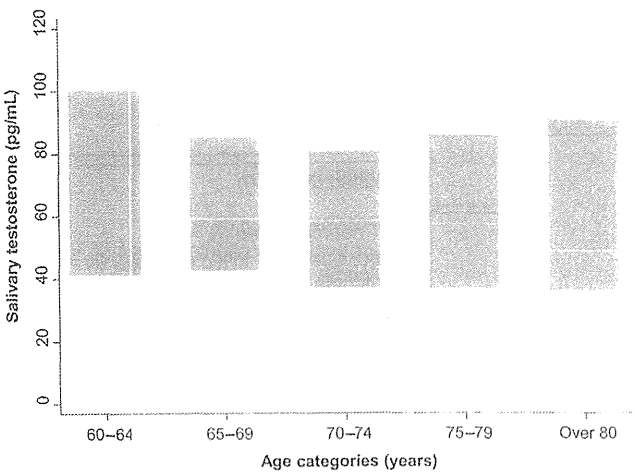

Fig. 2. Box plots for salivary testosterone levels stratified by age categories. White line in the boxes indicates median of sT in each category. Top and bottom of the boxes indicate 75th and 25th percentiles of sT in each category, respectively. sT, salivary testosterone.

analysis set were similar to those among whole older men, except for with respect to exercise habit, age (slightly younger), and TUG value (slightly lower) (Supplementary Table 3).

In the covariate-adjusted restricted cubic spline model, the splines demonstrated a nonlinear relationship between sT and falls ($P = .0021$ for nonlinearity). The estimated shape of the sT is shown in Figure 3, suggesting that the lower the sT level, the greater the likelihood of having any fall, citing 90th percentile of sT as a reference. In this model, the adjusted ORs of depressive symptoms for any fall were 3.49 [95% confidence interval (CI), 1.52–8.04]. We noted no apparent effect modification by depressive symptoms on the association between the sT and any fall ($P = .079$ for interaction).

To estimate the strength of the association of combination of sT levels and depressive symptoms, estimated ORs of combination of a given sT and depressive symptoms were shown in Table 2. Compared

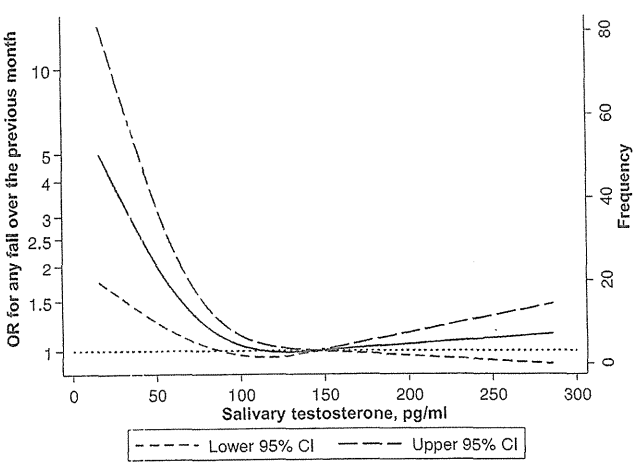

Fig. 3. Adjusted odds ratio (OR) of any fall over the previous month in men aged over 60 years.[a] CI, confidence interval.
[a]Logistic regression analysis with restricted cubic spline adjusted for covariates (age, body mass index, exercise habit, living alone, timed up and go, depressive symptoms, incontinence, hypertension, diabetes, cerebrovascular disease). Reference was set as 90th percentile of the salivary testosterone level (ie, median of the fifth quintile). The left vertical axis shows OR in log scale. Solid line indicates point estimates of OR. Dotted lines indicate CI. Gray bars indicate frequency of the salivary testosterone values. The right vertical axis shows frequency of each gray bar.

Table 2
Adjusted Odds Ratio (OR) of Any Fall Over the Previous Month in Men Aged Over 60 Years[a]

Salivary Testosterone		Adjusted OR (95% CI) for Any Fall Over the Previous Month	
Percentile	pg/mL	Participants Without Depressive Symptoms	Participants With Depressive Symptoms
5th	21.8	4.23 (1.66–10.8)	14.8 (3.76–58.0)
10th	26.3	3.74 (1.58–8.83)	13.1 (3.54–48.2)
30th	43.1	2.39 (1.34–4.26)	8.35 (2.78–25.1)
50th	58.9	1.67 (1.17–2.38)	5.83 (2.23–15.3)
70th	80.3	1.21 (1.03–1.43)	4.23 (1.77–10.1)
90th	146.5	1 [reference]	3.49 (1.52–8.04)
95th	211.4	1.07 (0.95–1.20)	3.72 (1.60–8.70)

CI, confidence interval.
[a]Logistic regression analysis with restricted cubic spline adjusted for covariates (age, body mass index, exercise habit, living alone, timed up and go, depressive symptoms, incontinence, hypertension, diabetes, cerebrovascular disease). Combination of 90th percentile of the salivary testosterone level (ie, median of the fifth quintile) and not having depressive symptoms was cited as reference.

with 90th percentile of sT, lower sT is associated with greater likelihood of having any fall. For example, OR for any fall in 5th percentile of sT is 4.23-fold (95% CI, 1.66–10.8). Compared with combination of 90th percentile of sT and no depressive symptoms, OR for any fall in combination of 5th percentile sT and depressive symptoms is 14.8-Zfold (95% CI, 3.76–58.0).

In sensitivity analysis using sT quintiles citing the top quintile as reference, the lowest quintile of sT is associated with greater likelihood of having any fall (Supplementary Table 4). Similarly, depressive symptoms were associated with an increased likelihood of having any fall, although this quintile model performed only slightly worse than the spline model (Supplementary Table 1). Another sensitivity analysis using a restricted cubic spline model among 762 participants showed similar associations between sT and increased ORs for any fall (Supplementary Figure 1). When CES-D was used as exposure instead of depressive symptoms, CES-D score was associated with any fall (Supplementary Table 5).

Discussion

In this cross-sectional study of community-dwelling older men, low testosterone levels were independently associated with any falls over the previous month. We also observed an increased association between depressive symptoms with any fall. In addition, combination of low testosterone levels and depressive symptoms had stronger association with falls than either parameter alone. These findings suggest that clinicians should be aware of the increased risk of falls in older men with testosterone deficiency or depressive symptoms.

Our findings regarding the relationship between low testosterone levels and increased likelihood of falling concur with results from previous studies. A study in France among adults aged 50–85 years found that low free testosterone levels were associated with increased likelihood of suffering falls over the last year (OR of decreased level of free testosterone vs normal level, 1.54).[11] Similarly, reduced bioavailable testosterone levels were found to be associated with increased likelihood of suffering falls in the future among adults in the United States aged 65–99 years (risk ratio of the lowest quartile of bioavailable testosterone vs the highest quartile, 1.40).[10] Other studies also noted an association between low total testosterone levels and increased likelihood of suffering falls in the future among adults in the United States aged over 65 years (OR of the highest quartile of total testosterone vs the lowest quartile, 0.22).[9]

However, conflicting results have also been reported. For example, a study in The Netherlands noted no association between total

testosterone levels and incident falls among adults aged 65–88 years.[15] Such conflicting findings may be explained in part by differences between measured fractions of circulating testosterone and ones in commercial assays, as well as by inclusion of depressive symptoms and other confounding factors for adjustment. As such, increased likelihood of suffering a fall among individuals with low testosterone levels may be due to their increased likelihood of having depressive symptoms in studies where such symptoms are not assessed. Only in a study in The Netherlands, the relationship between testosterone level and falls was evaluated with statistical adjustment for presence of depressive symptoms. In addition to these previous findings, our present findings here further noted that joint effect of low testosterone levels and depressive symptoms on falls in combination compared with the joint reference category (90 percentile of sT and no depressive symptoms) had multiplicative effect on falls (ie, each exposures was independently associated with falls). In addition, using splines, we noted a continued increase in risk of falling among participants with relatively low testosterone levels; by definition, quartiles or quintiles cannot detect an increase in risk below the 25th centile or 20th centile of exposure, respectively.[25]

We believe that our findings here will influence the activities of physicians and health-policymakers for several reasons. First, both low testosterone levels and depressive symptoms are potentially modifiable risk factors for falls. Testosterone deficiency can be managed with testosterone replacement therapy, and depressive symptoms can be managed with a combination of cognitive behavioral therapy and antidepressants; individuals with both testosterone deficiency and depressive symptoms may be able to manage their condition with a combination of these therapies. Physicians who encounter individuals with suspected testosterone deficiency should, therefore, carefully assess the presence of depressive symptoms to reduce further risk of falls. An international survey conducted among physicians treating testosterone deficiency showed that depressive symptoms are considered to be one of the main symptoms, other than sexual problems, related to testosterone deficiency—a finding that supports the potential coexistence of depressive symptoms with testosterone deficiency.[14] Second, screening for low testosterone levels in the saliva using ELISA may be a reasonable health plan for community-dwelling older men to stratify the fall risk, as ELISAs are more cost-efficient ($5 per sample) and easier to perform than radioimmunoassay and liquid chromatography/mass spectrometry.[26] Third, any biological connection between low testosterone levels and falls may be independent of mobility function, as we estimated the relationship between testosterone and falls with adjustment for TUG, which reflects gait, balance, and mobility. For example, reduced cognitive function may be involved as a nonmobility-related intermediate pathway, as low testosterone levels may be associated with visuospatial ability or vigilance.[27,28]

Several strengths to the present study warrant mention. First, we demonstrated the relationship between testosterone and falls among community-dwelling older adults, adjusting for confounding variables such as depressive symptoms and TUG, which are potentially related to both testosterone and falls. Second, we showed that the strength of the association between combination of low testosterone level and depressive symptoms and falls might be larger than that of low testosterone or depressive symptoms alone; specifically, the strength of the association appears to be equal to the product of the 2 exposures in terms of OR. These findings provide a basis for thoughtful consideration of how to reduce risk of falls in older men with both testosterone deficiency and depressive symptoms.

However, several limitations to the present study also warrant mention. First, although sT is a reliable and suitable metric for evaluating testosterone levels in population-based studies,[29–31] the clinical guideline for the diagnosis of hypogonadism does not recommend its clinical use, as the methodology has not been standardized and adult male ranges are not yet available in most hospital or reference laboratories.[32] Therefore, in actual clinical practice, serum testosterone levels should be measured to diagnose hypogonadism. Further prospective studies are warranted to determine whether or not late-onset hypogonadism diagnosed via serum test and depressive symptoms are jointly associated with falls. The prevalence of late-onset hypogonadism is also known to rise with increasing body mass index (BMI) and number of coexisting illnesses. Median BMI in our population was much lower than mean values reported in western countries.[9,11,13] However, a study among Korean men aged 21–79 years showed that the participants' mean BMI was 24.5, and that even in the lowest quintile by serum testosterone level (113–378 ng/dL), BMI was 25.2.[33] Given these previous findings, hypogonadism among Asian people diagnosed by blood testing may be found among individuals with relatively low BMI more often than among Caucasians with BMI in the same range. Further, some endocrine specialists question the validity of sT measured by ELISA. However, previous studies have shown that sT levels obtained via ELISA share good correlation with those obtained via liquid chromatography/mass spectrometry,[26] and sT has also been shown to be closely correlated to serum free testosterone.[34] However, in addition to differences noted based on assay adopted, blood contamination in saliva might also influence testosterone concentration.[35] As such, in the present study, saliva with suspected blood contamination was excluded from analyses. Even taken together with these drawbacks, however, utilization of sT still facilitates easily conducted, minimally invasive screening methods for evaluating testosterone levels on a population basis. Second, nonprescriptional use of testosterone or methyl-testosterone could not be recorded. However, use of such medication in our population is unlikely, as these compounds require a physician's prescriptions and are not available as over-the-counter drugs in Japan. Third, the cross-sectional design of the present study means that we cannot attribute causality from the associations between testosterone and depressive symptoms and falls. Although we believe that low testosterone as a cause of falling is biologically plausible, association between low testosterone or depressive symptoms and falls might be explained by reverse causality. Fourth, we were unable to include other medication usage and all chronic conditions in our analyses, and given that use of antihypertensives, sedatives, or antidepressants are also potential risk factors for falls,[4,36] the association between salivary testosterone and falls in the present study might be confounded by these factors. To mitigate this limitation, we adjusted for individuals with hypertensive problems. Effect of depressive symptoms on falls might be mediated partly by sedatives or antidepressants, as individuals with depressive symptoms are often prescribed these agents. The literature suggests that use of serotonin selective reuptake inhibitor is indeed associated with increased salivary testosterone levels,[37] and that serotonin selective reuptake inhibitor is associated with falls.[36] However, given that we adjusted for depression symptoms, we, therefore, believe it unlikely that any association between sT and falls was confounded by antidepressants. Although arthritis (including osteoarthritis) is prevalent in elderly and is also a potential risk factor for falls,[38] its burden on functional mobility should be reflected by TUG. As such, we believe that these confounding factors had negligible effects on our analyses. Fifth, a high rate of missing data was noted in the primary analyses. In sensitivity analyses using 87.7% of the older men in the health check-up examination showed an association similar to, but slightly smaller than, that noted in primary analyses between low sT and falls (Supplementary Figure 1). We, therefore, cannot completely exclude the possibility that our findings in the primary analysis may suffer from selection bias.

Conclusions

In conclusion, both lower testosterone and depressive symptoms were found to be separately associated with any falls over a 1-month period among community-dwelling older men. Furthermore, having both low testosterone levels and depressive symptoms might imbue a greater likelihood of having falls than either metric alone. Causality of these associations should be confirmed in future prospective studies with adjustment for potential confounding by more numbers of chronic illnesses.

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Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2013.11.003.

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特集　高齢者の薬物療法ガイドライン

臨床に役立つQ&A

2. 介護施設における薬物療法の優先順位をどのように考えたらよいでしょうか

松井　敏史　竹下　実希　井上慎一郎　里村　元　神﨑　恒一

Key words　介護施設　不適切薬剤投与(PIM)　薬剤有害事象(ADEs)　転倒　誤嚥性肺炎

介護施設での薬物療法の優先順位を探るべく先行研究のレビューを行った．多剤投与と不適切薬剤投与や薬剤有害事象には正の相関があり，精神科薬が多く関与していた．次に当科に介護施設から入院し，また退院した30名の投与薬物を調査した．患者は入院前に平均7.1種類の薬剤を使用していたが，入院によりビタミン薬・脂質異常症薬・抗尿酸薬の処方が減少した．また1臓器3剤以上の処方が認められた消化器系薬，降圧薬，精神科薬，利尿薬も減薬対象となっていた．したがって，①病態変化による薬剤継続の可否(ビタミン薬など)，②1臓器当たり3種類以上の薬剤，③精神科薬，④入院原因として最も多い誤嚥性肺炎を誘発する薬剤に留意し，患者のQOLを損なわない薬剤選択が推奨される．

はじめに

不適切薬剤投与(potentially inappropriate medication use：PIM)の問題は，介護施設入所者に端的に現れる．なぜなら彼らは，①薬剤代謝に関わる生理機能の低下した高齢者を体現し，②慢性疾患を多く抱えるためおそらく必要な薬剤数が多く，③認知症を発症していれば，とかく副作用が問題になる抗精神病薬が投与される可能性があるからである．これらは薬剤有害事象(adverse drug events：ADEs)の頻度を上げ，高齢者ではADEsへの対処の遅れ(ADEsの症状が非特異的であったり，患者の自覚症状や訴えの感度が低下することによる)が重なり，患者の命に関わるような重大な影響を及ぼす可能性さえある．

本来，薬物療法の優先順位は，①患者の疾患や病態の安定に寄与する薬剤を選びつつ，②PIMを避け，薬剤の主作用と副作用の折り合いがつけば理想である．しかし介護施設には，慢性疾患に対してどこまで薬剤を継続するかの問題，また施設によっては包括医療の，あるいは患者・家族側の経済上の問題が主治医の薬剤選択に影響し得る．これは時に，薬剤中止に伴う新たな有害事象を生み出す可能性を一方ではらむ．

本稿では，このPIMをキーワードにこれまでの論文をレビューし，筆者らの所属する高齢診療科の介護施設入所者からの入院者のデータを提示することで，介護施設における薬物療法の優先順位を探る．

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介護施設における薬剤の使用状況

1．なぜ，問題がPIMに関与するか

Beersらは1991年，PIMに関するクライテリア(Beers Criteria)を提唱し，不適切薬剤リストを掲げた．彼らは介護施設に入所する1,106名の薬剤投与状況を調査し，平均投与7.2種類の処方を受けていること，また患者の40%が少なくとも1種類の，10%が2種類以上のPIMがあると報告した[1]．Beers Criteriaはその後，2003年，2007年の改訂を経て，最新版(2012年版)はAmerican Geriatric Societyのホームページより入手可能である[2]（ポケット版：http://www.americangeriatrics.org/files/documents/beers/PrintableBeersPocketCard.pdf）．Beers Criteriaを用いた欧米の介護施設におけるPIMの頻度は15～70%と幅があるが，PIMに関与する要因としてまず，多剤投与(polypharmacy)が挙げられる[3]．Dhallらの介護施設入所者44,562名の検討では，薬剤が多くなればなるほどPIMが増加し，9種類以上の薬剤を服用する群は1～3剤の服用群に比べ，3.5倍であったと報告している．また，そのほかの患者側の要因として，女性・80歳未満・長期入所・低学歴・合併症の数を指摘している[4]．一方，施設側の要因として，ベッド数が多いこと，登録看護師対患者比率が低いこと，看護スタッフの入れ替わりが多いことなどが報告されている．

2．介護施設での多剤処方はADEsの増加につながる

多剤療法はADEsに関係する．Ruthsらの1,354名の介護施設入所者の検討では，投与薬剤数とADEsには正の相関が認められた[5]．同様に，Hosia-Randellらの報告では1,987名の施設入所者を検討し，薬剤相互作用(drug-drug interaction)に曝される患者は9種類以上の薬剤を服用し，特にクラスD(避けるべき相互作用)事象の過半数を占めていた[6]．また介護施設入所者のうち，抗不整脈薬あるいはパーキンソン病治療を行っている多剤服用者では，転倒関連の外傷が増えると報告した[7]．

3．介護施設での主要なPIMは精神科薬であり，ADEsを招く

介護施設のPIMには精神科薬が多く含まれることが特徴であり，抗精神病薬・3環系抗うつ薬・長期作用型のベンゾジアゼピンなどが多くの研究でPIMとして挙げられている[8]．その結果，精神科薬投与による不穏・徘徊・尿失禁・転倒・便秘といったADEsが多く報告されている[9,10]．これらの長期使用では，遅発性ジスキネジアや大体頸部骨折のリスク上昇，再転倒との関連や認知機能低下の問題が生じる[9]．

杏林大学付属病院高齢診療科での介護施設者の服薬状況調査

1．介護施設からの入院患者の薬剤使用状況

介護施設での薬剤療法を行う上で考慮すべきこととして，使用薬剤の種類を減らすこと，特に精神科薬の減薬はADEsを減らすようである．そこで，当科での介護施設における服薬状況を調査した．方法は，平成25年1月1日～12月31日までに杏林大学付属病院高齢診療科に入院した327名のうち，在宅からの入院患者(205名)と施設からの入院患者(72名)，計277名である．ここでは，調査期間中2回目以上の入院事象(38名)と病院からの転院患者7名，およびデータに不備がある5名は解析から除外した．

入院患者背景は次の通りである(表1)．介護施設者は平均5.2疾患を抱え，誤嚥性肺炎で入院する割合が高く，尿路感染・心不全を合わせると入院事象の6割に達する．介護施設に退院できない場合も4割以上にのぼる．また内服薬の種類は6剤であるが，在宅からの入院患者との間に差異は認めない(図1A)．しかし，疾患数と内服薬に関して在宅患者では正の相関がある一方，介護施設患者では疾患数と薬剤種類との間に関連は認められなかった(図1B)．

表1　杏林大学付属病院高齢診療科における介護施設からの入院患者背景

入院前	介護施設(72名)	在宅(205名)
年齢	87.1±5.0	86.3±5.9
性別(女性/男性)	41/31	126/79
疾患数	5.2±1.7*	4.8±1.7
入院事由(主要なもの)		
誤嚥性肺炎	29(40.3%)	44(21.5%)
気管支炎他肺疾患	6(8.3%)	10(4.9%)
市中肺炎	1(1.4%)	26(12.7%)
尿路感染・腎盂腎炎	11(15.3%)	27(13.2%)
心不全他心疾患	4(5.6%)	21(10.2%)
低ナトリウム血症	3(4.2%)	3(1.5%)
脱水・熱中症	2(2.8%)	11(5.4%)
入院日数	33.1±22.8	29.2±23.2
退院後行き先		
在宅	0(0%)	113(55.1%)
介護施設	42(58.3%)	28(13.7%)
病院・療養型病床群	22(30.6%)	40(19.5%)
死亡	8(11.1%)	24(11.7%)

*：p=0.06 by unpaired t-test

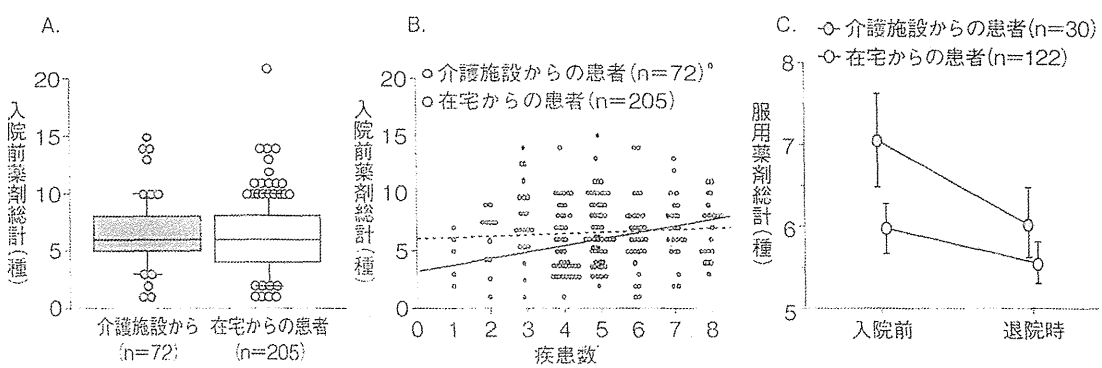

図1　介護施設からの入院患者の投与薬剤の特徴

A：介護施設からの入院患者の投与薬剤数の分布(箱ひげ図)．介護施設，在宅からの入院患者は6剤(中間値)を服用している．

B：疾患数と投与薬剤種類との関連．在宅からの患者では疾患数と投与薬剤数には正の相関がある(r=0.30，p<0.001)．一方，介護施設患者では関連を認めない(r=0.08，p=0.55)．実線は，在宅患者での回帰直線．

C：入院前後の薬剤数の変化．介護施設からの入院患者では平均1剤の減薬となった．

2．介護施設入所者の入院前後の薬剤変更

次に，72名の介護施設からの入院患者のうち，経口摂取が可能(内服治療が可能)なまま介護施設に退院した30名を対象に，入院前後の使用薬剤の調査を行った．入院前，対象者は平均7.1種類を服用しており，消化器系薬剤の服用者が多く(26名，87%)，降圧薬，抗血小板薬/抗凝固薬が続いた(表2)．また入院前には消化器系薬剤，降圧薬，精神科薬，利尿薬で3剤以上の処方が認められた．

これらの介護施設からの患者は，ビタミン薬・脂質異常症薬・抗尿酸薬が入院中に薬剤削

表2　介護施設からの入院患者30名の入院前後の内服薬内訳

	入院前(7.1±3.1剤)				退院時(6.1±2.3剤)				p値*
	処方人数	薬剤種類			処方人数	薬剤種類			
		1剤	2剤	3剤以上		1剤	2剤	3剤以上	
消化器系薬剤	26	5	11	10	28	10	11	7	0.58
降圧薬	17	8	6	3	22	8	12	2	0.15
抗血小板薬/抗凝固薬	16	15	1		17	16	1		0.71
精神科薬	12	9	1	2	10	9	1		0.23
中枢神経	11	11			4	4			0.01
泌尿器科薬	10	9	1		6	2	4		0.80
利尿薬	9	5	3	1	13	9	4		0.52
循環器科	8	7	1		6	6			0.26
栄養ビタミン製剤	6	6			2	2			0.04
脂質異常症薬	6	6			1	1			0.02
高尿酸治療薬	5	5			1	1			0.04
漢方薬	4	4			3	3			0.71
骨カルシウム代謝薬	4	4			1	1			0.08
鎮痛薬	3	3			4	4			0.66
糖尿病治療薬	3	2	1		2	1	1		0.33
呼吸器科	2	1	1		2	2			0.33
抗アレルギー薬	2	2			0				0.16
甲状腺ホルモン	2	2			3				0.33
抗菌薬	1	1			1				1
抗腫瘍薬	1	1			1	1			1
副腎皮質ステロイド	1	1			1	1			1
抗リウマチ薬	0				0				—
腎不全治療薬	0				0				—
免疫抑制薬	0				0				—

*paired t-testによる

減対象となり，また3剤以上の同一臓器に対する治療薬の処方が削減対象となっていた(表2)．その結果，退院時には全体で1剤の減薬となった(図1C)．一方，在宅から入院し在宅あるいは施設に退院した患者122名では，薬剤種類は入院前後で平均6種類から5.6種類にとどまっていた．

さらに，処方の多かった系統の薬剤に対し検討を行った(表3)．消化器科薬では，プロトンポンプ阻害薬(PPI)，セロトニン作動薬の処方増加が特徴で，一方H2ブロッカー，整腸剤は減薬対象になっていた．また，特筆すべきは精神科薬であり，ベンゾジアゼピン系の抗不安薬・睡眠薬の使用が削減対象となっていた．

薬剤療法の優先順位

先行研究や当科での薬剤調査から，以下のような薬剤選択が考えられる．

1．病態が変化した時に追加が必要な薬剤がある

当科での検討にあるように，ビタミン薬・脂質異常症薬・抗尿酸薬が減薬対象になっていた．これらは患者の栄養状態を含む全身状態の変化によって，薬物療法が見直された結果である．一方で，入院によりPPIの処方が増大している．これらは抗血小板薬や抗凝固薬が治療上必要な患者で，ほかの消化器病薬から切り替えら

表3　介護施設からの入院患者30名の入院前後の内服薬内訳

薬剤種類	入院前処方人数	退院時処方人数	増減
消化器系薬剤			
便秘薬/大腸刺激性下剤	13	15	＋2
便秘薬/塩類下剤	12	7	－5
胃薬 PPI	9	18	＋9
胃薬防御因子増強	8	5	－3
整腸剤	7	3	－4
胃薬 H_2 blocker	5	1	－4
肝疾患治療薬	3	2	－1
胃薬セロトニン作動薬	1	4	＋3
胃薬そのほか	1	0	－1
降圧薬			
降圧薬 Ca blocker	12	17	＋5
降圧薬 beta blocker	6	7	＋1
降圧薬 ARB	5	3	－2
ACEI	5	10	＋5
降圧薬 alpha blocker	1	1	0
精神科薬			
抗精神病薬非定型	4	3	－1
ベンゾジアゼピン抗不安薬	3	1	－2
睡眠薬短時間作用型	3	0	－3
非ベンゾジアゼピン睡眠薬	3	4	＋1
抗うつ薬 SSRI/SNRI	2	0	－2
睡眠薬長時間作用型	2	1	－1
抗うつ薬3環4環系そのほか	1	0	－1
チアプリド	0	1	＋1
抗精神病薬定型	0	1	＋1
利尿薬			
利尿薬ループ	7	11	＋4
カリウム保持性	4	4	0
サイアザイド系	3	2	－1

れた可能性がある．

2．1臓器当たり3種類以上の薬剤は削減対象になる

当科の調査では，1臓器当たり3種類以上の薬剤は削減対象になっていた(表2)．特に，消化器科薬・降圧薬・精神科薬は多剤投与がされており，1疾患1剤を基本に処方内容の見直しを進める．

3．精神科薬は処方内容を検討し，徐剤への変更や減薬を進める

最新の睡眠ガイドラインでは，高齢者にベンゾジアゼピン系睡眠薬を推奨していない[10]，ベンゾジアゼピン系薬剤や半減期の長い薬剤は，転倒につながる．また，抗精神病薬のシステマティックレビューによれば，8研究における抗精神病薬の休薬群と継続群の間で，精神症状の悪化に伴う離脱症状や，抗精神病薬の再使用に関して差がなかったと報告している[11]．精神科薬に関しては，①適応疾患に則った使用，②漫然と使用せず症状が安定したら休薬，③症状出

現時などに限った使用，(4)非薬物療法を検討する．

4. 嚥下機能を低下させ誤嚥性肺炎を起こしうる薬剤があれば削除する

自験例を挙げるまもなく，介護施設者の入院原因や経口摂取の可否に関わる最大の要因は，嚥下機能低下であり誤嚥性肺炎である[7]．嚥下機能を低下させる抗精神病薬は，認知症患者で誤嚥性肺炎のリスクを高める[8]．また，抗コリン作用や抗ヒスタミン作用のある薬剤は，注意力の低下や筋弛緩作用から嚥下機能を低下させるため，ベンゾジアゼピン系の抗不安薬などと並び，注意を要する薬剤である．これらの薬剤はいずれもBeers Criteriaに採用されており，中止や変更を検討する．

減薬へのそのほかの方策

1. スタッフの教育や薬剤に関わる多職種スタッフの参加

システマティックレビューによれば，介護施設におけるADEsを減らす介入が一定の効果を上げている[9]．スタッフの教育や多職種からなるチームミーティングを行うことで，使用薬剤数，使用量の減少につながる．

2. 薬剤スタッフとの連携

薬剤師からの薬剤使用に関する勧告は，主治医の処方変更や薬剤費の削減につながる[5]．Thompsonらによれば，臨床薬剤師が薬剤管理に全責任を負った場合，致死率・疾病率がいずれも改善し，平均2剤の投与薬剤減少につながるという[10]．PIMに関して，薬剤師と連携して経験を積み重ねることでADEsが減り，ひいては薬剤削減につながる可能性がある．

おわりに

介護施設は患者のcureよりcareを重視しており，根本治療よりも患者QOLが特に重視される場である．薬剤治療も患者のQOLを担うツールとしてとらえ，特に認知症患者では常に代替医療(非薬物療法)の可能性を探りながら，また薬剤療法を行う場合も多職種が連携し，PIMやADEsを減らす試みが必要である．

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Geriatric Medicine 次号予告(第52巻 第9号)

特集 高齢者における排尿障害

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治療　全人的医療を目指す

アルコールと認知症

松井敏史

はじめに

適度な飲酒は体に良いと一般に流布している。多くの観察研究で1日2ドリンク（純エタノール換算で20g）程度までの飲酒量でmortality ratesが一番低く、飲酒量とはJカーブの関係を取るとされる。2ドリンクとはビール500mL、日本酒だと1合に相当する。[1] 一方で、過多の飲酒は喫煙・肥満と並びpreventable deathに関与する3大原因の一つであり、健康被害を増大させる。[2]

それでは、アルコールと認知症にはいかなる関係があるであろうか。

認知症リスクとしてのアルコールの関与
―認知症発症とJカーブ

2000年以降、少量の飲酒には認知症発症低減効果があるとの大規模な前向き研究が相次いで発表された。

Mukamalらは、約5、900人のCardiovascular Health Studyの参加者を平均6年間追跡し、1週間当たり2から12ドリンクの飲酒者で最も認知症になる危険性が低く、オッズ比が0・46（95％CI：0・27～0・77）であったと報告している。[3] 最近の23研究を合わせたメタ解析では、少量飲酒に認知症のリスク低減効果が認め

られ、全認知症においてRisk ratio（RR）が0・63（95％CI：0・53～0・75）、アルツハイマー病では0・57（0・44～0・74）、脳血管認知症では0・82（0・50～1・35）と報告している。[4]

少量飲酒の効用として、HDLコレステロール増加作用、フィブリノーゲン低下作用、内因性エストロゲン活性化、また特にワインにおけるポリフェノールやレスベラトロールの抗酸化作用などがあげられる。

アルコールと脳画像所見―住民研究より

健康高齢者において、習慣飲酒（週に3日以上、1日当たり2ドリンク）は脳血管障害のリスク因子である。自験例では、65歳以上の健康者を対象にした住民検診で、MRI画像上の径5㎜以上の無症候性脳梗塞の頻度は約25％であり、そのリスク因子は年齢・高血圧・喫煙・飲酒・男性・血漿ホモシステイン値であった。[5]

またTakiらによれば、高齢者住民の調査で、生涯アルコール飲酒量とMRI上の脳容積には逆相関が認められ、特に中前頭回領域で顕著であるという。[6]

つまり、脳血管障害・脳萎縮共に、飲酒量との関係はJカーブではなく、飲めば飲むほど悪化するという負の相関にある。

アルコール依存症者の認知機能と脳画像所見

アルコールの関与する認知症を、包括的にアルコール関連認知症（Alcohol-related dementia）と呼ぶ（表①）[7]。毎日6ドリンク（ビールで1、500mL、日本酒で3合）を超える多量飲酒者は本邦では860万人、そのうちアルコール依存症者は80万人と推定されるが[8]、これらの者がJカーブの恩恵を受けることはなく、加齢とともに認知機能低下が顕在化する。

高齢になるとアルコール依存症者は認知機能低下が一般的であり、認知機能のMini-Mental

①アルコールによって引き起こされる代表的な神経系の合併症とその症状

Ⅰ. アルコールの急性の作用
- 酩酊、泥酔、昏睡などの急性アルコール中毒、外傷性脳出血病変、大酒家突然死症候群

Ⅱ. アルコールの慢性の作用

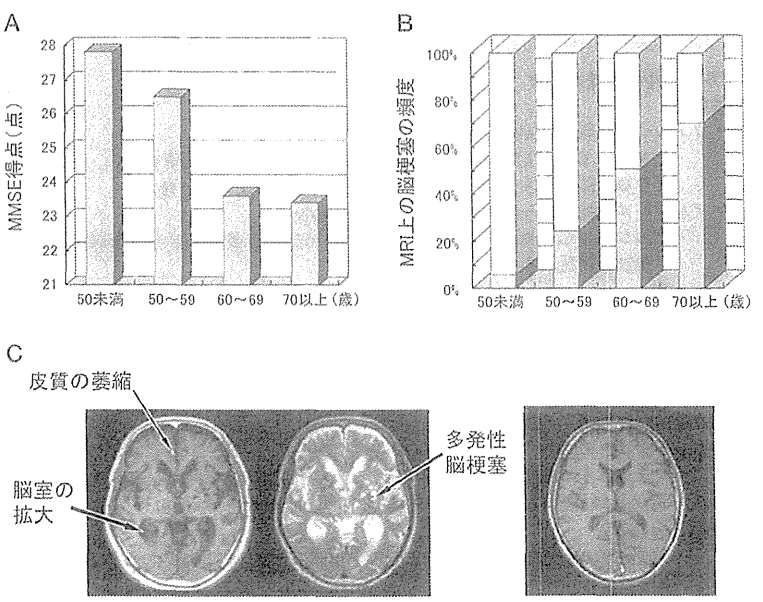
急性発症
- ウェルニッケ脳症（Wernicke's encephalopathy）
  - ビタミンB_1欠乏によって引き起こされる急性の脳症。痙攣を伴い、眼球運動異常や歩行障害をきたす。回復しても健忘症が後遺症として残る
- アルコール離脱に伴う振戦・せん妄・痙攣・幻覚
  - アルコール依存症状態の後のアルコールの急速な変化により、神経伝達物質の平衡状態が乱れる
- その他
  - Marchiafava-Bignami 病、中心性橋延髄髄鞘崩壊症
  - 脱水・電解質異常・低血糖など全身状態悪化に伴うもの
  - 肝性脳症
  - 痙攣発作

慢性の経過（アルコール関連認知症を含む）
- コルサコフ症候群
  - ウェルニッケ脳症の後遺症として、あるいは脳症がなくとも、健忘症が長期にわたって継続する
- 末梢神経障害
  - 両側性の感覚神経の鈍麻やしばしば筋萎縮を伴った運動神経障害をきたす
- アルコール性小脳変性症
  - 小脳が萎縮することにより、歩行時の不安定が持続する
- その他
  - 外傷の後遺症、合併する脳血管障害など

大量のあるいは長期にわたるアルコール飲酒は神経系に多彩な急性・慢性変化を及ぼす。

State Examination（MMSE）を行うと、60歳代ですでに認知症の初期段階にある（図②A）。これはアルツハイマー病の平均発症年齢より10歳も若い。頭部MRI上、萎縮性変化（前頭葉萎縮や脳室（側脳室、第3、4脳室）拡大・脳溝の開大など）が認められ、高齢者では脳梗塞・深部白質病変が顕著になる（図②C）。脳梗塞の頻度は60歳代で50％と、健康高齢者の3～4倍の頻度に上る（図②B）[9,10]。また、ビタミンB_1や葉

②アルコール依存症者の認知機能(A)、頭部 MRI 上の脳梗塞の頻度(B)
（アルコール依存症患者242人の調査）と典型例の MRI 画像（C）



A.アルコール依存症では50歳代ですでに軽度認知機能障害（26.5点）を認め、60歳代では認知症の初期状態の得点（23.5点）である。
B.頭部 MRI 上、60歳代ではすでに半数の患者において脳梗塞が認められる。
C.アルコール依存症患者の MRI 画像（左）と同年代の健康者の MRI 画像（右）。
患者は入院時60歳代前半の男性。60歳で定年退職し、その後量酒が習慣化。次第に酩酊時の転倒、失禁、歩行異常がみられるようになり入院。MRI 上は脳室の拡大や皮質の萎縮を認め、基底核を中心とした小梗塞が多発。深部白質には T2高信号が散在しているパターン。MMSE は25/30と境界レベル。

酸が低下する例が多く、栄養因子の関与がうかがわれる。

この栄養障害が端的に現れるのがコルサコフ症候群（Korsakoff's syndrome）であり、記銘力障害・見当識障害・作話を症状とする代表的なアルコール関連認知症である。[11] 他の認知症性疾患との相違点は、代謝性（アルコールや栄養因子が関与する）であって可逆性（reversible あるいは treatable）な側面があり、比較的若年発症である点である。[12] もっとも、コルサコフ症候群の原因はアルコールそのものではなくビタミンB_1欠乏であり、アルコール依存症者でなくとも発症する。しかし、コルサコフ症候群の多くがアルコール依存症者なのは、彼らがしばしば連続飲酒から食事も摂らず、その結果ビタミンB_1欠乏に陥るためである。

その他のアルコール依存症者のMRI所見として、約1,500症例の検討では、脳挫傷や硬膜下血腫は3・5%に、認知機能に関係する視床・被殻の出血性病変も3・5%に、外傷後水頭症様の所見も1・9%に認められる。重度肝障害をうかがわせるT1強調画像での淡蒼球の高輝度は、19%に上る。[13]

高齢者における飲酒問題の特徴と飲酒指導

アルコール依存症者でなくとも高齢者の約15%に飲酒が関連した何らかの健康問題があるといわれ、アルコール関連認知症につながる予備軍の裾野は広い。また、アルコール関連認知症は、健康寿命に関わる重大な疾患としても捉えられる。[14] 脳血管障害そのものが、転倒・肺炎にもつながり、寝たきりを生ずる4大疾患が、骨折転倒・廃用症候群・脳血管障害・認知症であることを考えると、多量飲酒はどの疾患にも直接・間接に関与することが想像できる。

高齢者では、ライフスタイルの変容が飲酒の意義を変質させ、飲酒そのものが目的となる。すなわち、かつては仕事上の付き合いなど社会