

findings show non-HDL-C might be an important risk factor for stroke, even in elderly diabetes patients.

We also showed that non-HDL-C predicted diabetes-related mortality and total diabetes-related events. The predictive power of non-HDL-C for mortality was stronger in high-risk CHD patients associated with vascular intervention, chronic renal failure or diabetes mellitus.^{11–15} In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) trial on acute coronary syndrome patients receiving either pravastatin 40 mg or atorvastatin 80 mg, non-HDL-C, HDL/TC and Apolipoprotein (Apo) B / Apo A1 predicted death or acute coronary events.¹¹ In the Bypass Angioplasty Revascularization Investigation (BARI) Study, non-HDL-C was a strong and independent predictor of non-fatal MI and angina pectoris at 5 years compared with LDL-C or triglycerides, even after adjustment for potential covariates in patients undergoing angioplasty revascularization or bypass-surgery.¹² Nishizawa *et al.* showed that non-HDL-C in predialysis serum was a significant and independent predictor of cardiovascular mortality in hemodialysis patients.¹³ In the European Community funded Concerted Action Programme into the epidemiology and prevention of diabetes (EURODIAB) Prospective Complication Study, non-HDL-C, age, pulse pressure and waist-to-hip ratio were independent predictors for all-cause mortality in type 1 diabetes patients.¹⁴ Herman *et al.* showed the discriminatory power of non-HDL-C was similar to Apo-B in diabetes patients because of the discriminant ratio and unbiased equation of equivalence.¹⁵ Non-HDL-C was also shown to be a better predictor of CVD mortality or acute myocardial infarction (AMI) than LDL-C or TC.^{16–18} In the present study, the predictive potential of non-HDL-C was stronger in diabetic patients who had a residual risk beyond LDL-C.

Our finding in the landmark study that patients with a non-HDL-C > 163 mg/dL had a significantly increased incidence of stroke, diabetes-related death and total events compared with those with a non-HDL-C < 122 mg/dL suggests that lipid lowering with a statin is of considerable importance, even in the elderly diabetes patients. This result is in agreement with a report from the Japanese Circulatory Risk in Communities Study¹⁹ showing an association between non-HDL-C and CHD incidence, with the greatest discriminative power at non-HDL-C > 140 mg/dL. In contrast, in the National cholesterol education program-III (NCEP-III) guidelines, the optimal goal of non-HDL-C in CHD patients was <100 mg/dL.¹⁷ The decrease in non-HDL-C after the landmark time in both our intensive and conventional treatment groups might represent an effect of statin treatment, and might also explain the differences in events described here. In the Collaborative Atorvastatin

Diabetes Study, treatment decreased both LDL-C and non-HDL-C, leading to prevention of stroke and cardiovascular events.²⁸ The present results suggest that even in elderly high-risk diabetes patients, a reduction of non-HDL-C using a statin might be beneficial for preventing CVD, stroke and mortality.²⁹

The reason for the lack of significant associations between non-HDL-C and cardiovascular events remains unclear. In contrast, LDL-C was a significant predictor of cardiovascular events in the present study. The differences in predictive power of non-HDL-C and LDL-C for CVD and stroke might reflect variability in the vulnerability of cerebral and coronary arteries to lipoproteins. Non-HDL-C in combination with a Apo-B100, remnant lipoproteins and small, dense lipoproteins might be involved in stroke events as a consequence of biological actions beyond LDL-C. Alternatively, the predictive power of non-HDL might be affected by age,²⁰ sex,^{21,22} ethnicity²³ and lifestyle habits.

The present data showed high HbA1c predicted stroke in elderly people with type 2 diabetes. In a Finnish elderly cohort, HbA1c and fasting, and 2-h glucose predicted stroke events.³⁰ In the Diabetes among Indian Americans (DIA) study, HbA1c and smoking were predictors for stroke in men without previous stroke, whereas therapy with insulin plus oral agents predicted stroke in men with a history of stroke.³¹

In contrast, stroke incidence in the present study was lowest in the second lowest HbA1c quartile (7.3–7.9%), resulting in a J-curve incidence for stroke according to HbA1c distribution. The study on the UK General Practice Database showed low and high HbA1c were both associated with increased large-vessel disease and all-cause mortality in 27 965 diabetic patients,³² possibly because of hypoglycemia, leading to arrhythmia, cardiovascular autonomic abnormalities, QT prolongation, and induction of prothrombotic and proinflammatory markers. Moderately abnormal glucose control with HbA1c around 7.5% (JDS, 7.1%) with no hypoglycemia during follow up might have a beneficial effect on stroke in high-risk, elderly diabetic patients.

Similarly, the lowest incidence of stroke and total diabetes events in the second lowest SBP quartile (127–136 mmHg), and the lowest incidence of cardiovascular events and total diabetes events in the second lowest LDL-C quartile (99–116 mg/dL) suggest the existence of a J-curve. The J-curve effect of BP lowering has been reconsidered recently, with recommendation that aggressive BP control should be undertaken carefully in high-risk, older diabetes patients.^{33,34} A review of observational studies shows a trend where all-cause mortality was highest when TC was lowest.³⁵ Only a few randomized control trials have not provided evidence of an effect of lipid-lowering treatment on mortality in ≥80 years-of-age patients.³⁵ Although it is not possible

to disregard the possibility that comorbidities, such as inflammation and malnutrition, are associated with an increased incidence of stroke in the lowest SBP and LDL-C groups, cautious and comprehensive management of BP and LDL-C is also required in older people with diabetes.

The present study had several limitations. First, our cohort comprised high-risk, elderly Japanese subjects, and therefore our results cannot be generalized to other populations. Second, the study population was limited by a relatively small sample size compared with other published reports, and it is likely that the lack of significant relationships between variables reflects inadequate statistical power rather than a true negative result. Finally, the landmark analysis after 1 year of intervention did not completely reflect the effects of temporal changes in the parameters over the entire follow-up period, although some tracking effects of lipid parameters were observed.

In conclusion, this relatively large-scale prospective study showed non-HDL-C was an important predictor for stroke, diabetes-related mortality and total diabetes events in high-risk, elderly type 2 diabetes patients. Non-HDL-C reflected several pathological lipoproteins, including LDL-C, ApoB, triglycerides, remnant lipoproteins and small, dense lipoproteins.³⁶ Measurement of non-HDL-C might therefore be useful for evaluating the effects of lipid intervention using statin, fibrates and eicosapentaenoic acid in elderly people with diabetes. However, further studies including sophisticated randomized trials are necessary to elucidate the role of non-HDL-C on vascular events.

Acknowledgments

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Conflict of interest

There is no conflict of interest. The Japanese Elderly Diabetes Intervention Trial (J-EDIT) Study Group has not cleared any potential conflicts.

References

- 1 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–853.
- 2 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703–713.
- 3 Ohkubo Y, Kishikawa H, Araki E *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; **28**: 103–117.
- 4 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383–393.
- 5 Gerstein HC, Miller ME, Byington RP *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.
- 6 Duckworth W, Abraira C, Moritz T *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129–139.
- 7 Pop-Busui R, Evans GW, Gerstein HC *et al*. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. *Diabetes Care* 2010; **33**: 1578–1584.
- 8 Bittner V. Non-high-density lipoprotein cholesterol: an alternate target for lipid-lowering therapy. *Prev Cardiol* 2004; **7**: 122–126.
- 9 Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P *et al*. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; **302**: 1993–2000.
- 10 Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM. Lipid levels and the risk of ischemic stroke in women. *Neurology* 2007; **68**: 556–562.
- 11 Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol* 2009; **29**: 424–430.
- 12 Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G, Bypass Angioplasty Revascularization Investigation. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 2002; **106**: 2537–2542.
- 13 Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH, EURODIAB Prospective Complications Study Group. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). *Diabetes Care* 2008; **31**: 1360–1366.
- 14 Nishizawa Y, Shoji T, Kakiya R *et al*. Non-high-density lipoprotein cholesterol (non-HDL-C) as a predictor of cardiovascular mortality in patients with end-stage renal disease. *Kidney Int Suppl* 2003; **84**: S117–S120.
- 15 Herman MP, Sacks FM, Ahn SA, Rousseau MF. Non-HDL-cholesterol as valid surrogate to apolipoprotein B100 measurement in diabetes: discriminant ratio and unbiased equivalence. *Cardiovasc Diabetol* 2011; **10**: 20.
- 16 Cui Y, Blumenthal RS, Flaws JA *et al*. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 2001; **161**: 1413–1419.

- 17 Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol* 2008; **101**: 1003–1008.
- 18 Tanabe N, Iso H, Okada K *et al.* Japan Arteriosclerosis Longitudinal Study Group. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events – the JALS-ECC. *Circ J* 2010; **74**: 1346–1356.
- 19 Kitamura A, Noda H, Nakamura M *et al.* Association between non-high-density lipoprotein cholesterol levels and the incidence of coronary heart disease among Japanese: the Circulatory Risk in Communities Study (CIRCS). *J Atheroscler Thromb* 2011; **18**: 454–463. Mar 3. [Epub ahead of print].
- 20 Bruno G, Merletti F, Biggeri A *et al.* Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. *Diabetologia* 2006; **49**: 937–944.
- 21 von Mühlen D, Langer RD, Barrett-Connor E. Sex and time differences in the associations of non-high-density lipoprotein cholesterol versus other lipid and lipoprotein factors in the prediction of cardiovascular death (The Rancho Bernardo Study). *Am J Cardiol* 2003; **91**: 1311–1315.
- 22 Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Ohta H. Association between non-high-density lipoprotein cholesterol concentrations and mortality from coronary heart disease among Japanese men and women: the Ibaraki Prefecture Health Study. *J Atheroscler Thromb* 2010; **17**: 30–36.
- 23 Akerblom JL, Costa R, Luchsinger JA *et al.* Relation of plasma lipids to all-cause mortality in Caucasian, African-American and Hispanic elders. *Age Ageing* 2008; **37**: 207–213.
- 24 Araki A, Iimuro S, Sakurai T *et al.* and the Japanese Elderly Intervention Trial Research Group: long-term multiple risk factor interventions in Japanese elderly people with diabetes mellitus: the Japanese Elderly Intervention Trial (J-EDIT): study design, baseline characteristics, and effects of intervention. *Geriatr Gerontol Int* 2012; **12** (Suppl. 1): 7–17.
- 25 Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG index of Competence. *Arch Gerontol Geriatr* 1991; **13**: 103–116.
- 26 Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–193.
- 27 Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol* 1986; **5**: 165–173.
- 28 Colhoun HM, Betteridge DJ, Durrington PN *et al.*, the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomised placebo-controlled trial. *Lancet* 2004; **364**: 685–696.
- 29 Xu K, Han YL, Jing QM *et al.* Lipid-modifying therapy in diabetic patients with high plasma non-high-density lipoprotein cholesterol after percutaneous coronary intervention. *Exp Clin Cardiol* 2007; **12**: 48–50.
- 30 Kuusisto J, Mykkanen L, Pyorala L, Laakso M. Non-insulin dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke* 1994; **25**: 1157–1164.
- 31 Giorda CB, Avogaro A, Maggini M *et al.* The DAI study group. Incidence and risk factors for stroke in type 2 diabetic patients. The DAI Study. *Stroke* 2007; **38**: 1154–1160.
- 32 Currie CJ, Peters JR, Tynan A *et al.* Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; **375**: 481–489.
- 33 Chrysant SG. Current status of aggressive blood pressure control. *World J Cardiol* 2011; **3**: 65–71.
- 34 Sleight P, Redon J, Verdecchia P *et al.* Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens* 2009; **27**: 1360–1369.
- 35 Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+ year old. *Age Ageing* 2010; **39**: 674–680.
- 36 Vasudevan MM, Ballantyne CM. Advances in lipid testing and management in patients with diabetes mellitus. *Endocr Pract* 2009; **15**: 641–652.



LETTERS TO THE EDITOR

New dorsiflexion measure device: A simple method to assess fall risks in the elderly

Dear Editor,

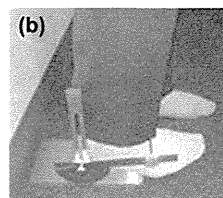
Hip fracture is the third leading cause yielding bedridden status in Japan, and more than 80% of hip fractures are reported to be caused by falling. There are a variety of causes for falls in the elderly, and one of the significant causes is the inability to lift their toes when they walk. Here, we show a new device to measure dorsiflexion angle, an instrument that we developed to assess fall risks in the elderly.

Participants were requested to stand up straight and step back until the hip leaned on the wall (Fig. 1a). The fulcrum of the instrument was adjusted to the center of the external malleolus (Fig. 1b). The arm of the instrument was set to stay level, adjusting the branching thin arm placed on the ridge of the dorsum of the foot. Then, participants were asked to dorsiflex as much as possible. The mean time to measure bilateral dorsiflexion angles was within 5 min.

We measured dorsiflexion and Fall Risk Index (FRI),^{1,2} including the history of falls within the past year, in 131 women (46–89 years, mean age 78.0 ± 7.1 years) and 88 men (46–93 years, mean age 76.2 ± 8.6 years) who visited the fall prevention clinic in Kyorin University Hospital. The occurrence of falls within the past year was 35.6%. Falls occurred 2.0 ± 0.1 times in fallers within 1 year, and women fell more frequently than men (42.7% vs 25.0%, $\chi^2 = 7.2$, $P \leq 0.01$). The average FRI score was 6.7 ± 3.4 in non-fallers and 10.6 ± 3.0 in fallers ($P < 0.0001$). Women showed a higher FRI score than men (8.8 ± 3.6 vs 7.0 ± 3.8 , $P = 0.003$).

This new device appears promising in detecting the high-risk group of fallers, because the dorsiflexion angle was significantly smaller in fallers than non-fallers (right 9.6 ± 8.4 vs 13.7 ± 9.6 degrees, $P = 0.012$; left 10.0 ± 8.5 vs 14.2 ± 9.8 degrees, $P = 0.014$). Furthermore, the occurrence of falls was more frequent as the dorsiflexion angle decreased in women ($\chi^2 = 6.4$, $P = 0.042$; Fig. 1c), and half of the subjects, whose dorsiflexion angle was less than 10 degrees, experienced falls within a year.

Previously, it was reported that hip fractures occur more frequently in women than men, even though the incidence rate of falls was comparable until the age of 90 years. This is considered to be a result of the higher prevalence of osteoporosis in women.³ In contrast, the present study found that women less than 90 years-of-age fell more frequently than men in the Japanese population of this age group. We also found that the FRI score was higher in women than men, as has been shown previously.⁴ In addition, dorsiflexion angle was



(c) Dorsiflexion and Fall

(n=219, Fall prevention clinic, Kyorin University Hospital)

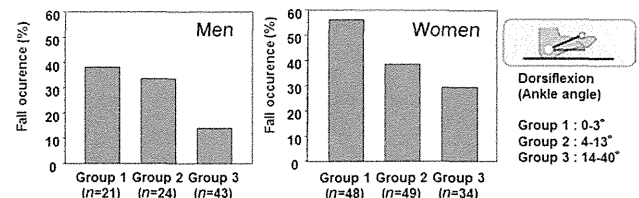


Figure 1 (a,b) How to measure dorsiflexion angle using a dorsiflexion measure device. (c) The relationship between dorsiflexion angle and the occurrence of falls within the past year. In men and women respectively, participants were grouped by tertile according to the dorsiflexion angle.

smaller in women than men (right 10.3 ± 8.4 vs 15.2 ± 10.1 degrees, $P = 0.0001$; left 11.0 ± 8.5 vs 15.2 ± 10.4 degrees, $P = 0.0013$), and a stepwise increase in the fall occurrence rate according to the level of dorsiflexion angle was evident in women (not significant in men). These results show that less ability to dorsiflex would partly explain the sex difference in the occurrence of falls and ensuing hip fracture.

The new dorsiflexion measure device we report here is easy and less time-consuming to use, and will be sure to help identify a high-risk group of fallers in the elderly.

Disclosure statement

This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients. All authors contributed significantly to this work and are

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References

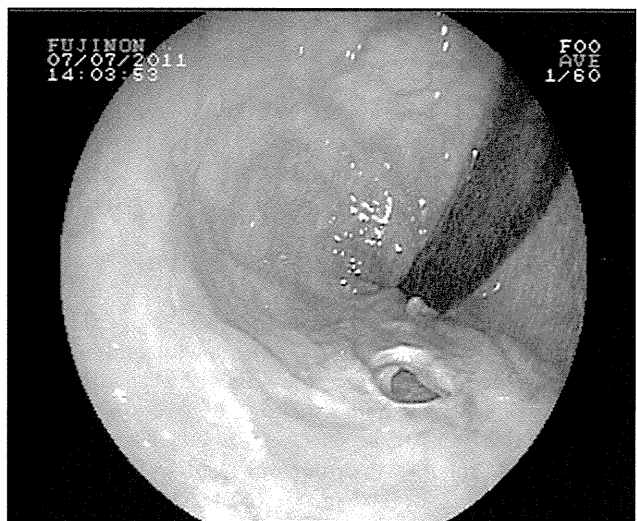
- Okochi J, Toba K, Takahashi T. Simple screening test for risk of falls in the elderly. *Geriatr Gerontol Int* 2006; **6**: 223–227.
- Wada T, Ishimoto Y, Matsubayashi K. Twenty-one-item fall risk index predicts falls in elderly community-dwelling Japanese. *J Am Geriatr Soc* 2009; **57**: 2369–2371.
- Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. *Age Ageing* 1990; **19**: 136–141.
- Ishimoto Y, Wada T, Matsubayashi K. Age and sex significantly influence fall risk in community-dwelling elderly people in Japan. *J Am Geriatr Soc* 2009; **57**: 930–932.

Rectal perforation as a result of self-administration of retrograde enema in an elderly dementia patient

Retrograde cleansing enemas are commonly used in the treatment of chronic constipation, especially in the elderly.¹ We report a case of colorectal perforation as a result of self-administered retrograde water enema in an elderly dementia patient.

A 76-year-old chronically constipated man was admitted to Türkiye Yuksek İhtisas Hospital Gastroenterology Department in Ankara, Turkey, with a 1-week history of rectal pain. His medical history showed he had the diagnosis of dementia. Clinical examination at that time showed normal vital signs, on examination of the abdomen there was no defense or rebound, digital examination was normal, and respiratory and circulatory system examinations were normal. All laboratory investigations including full blood count, serum amylase, liver function tests, urea and electrolytes were within normal limits. There was no abnormality in abdominal X-ray and abdominal ultrasonography. He was started on a retrograde enema by his family practitioner 7 days earlier for constipation. He described that the pain was precipitated by the first self-administration of the retrograde irrigation enema and the patient denied subsequent use. A preplanned colonoscopy was carried out, and on retroflexion a rectal perforation was detected (Fig. 1). An abdominal computed tomography scan showed perirectal air. Conservative management with intestinal rest and intravenous antibiotics was carried out. The clinical course of the patient was favorable without sepsis or generalized peritonitis. He was discharged home after a 7-day inpatient stay.

Perforation of the rectum and sigmoid colon caused by cleansing enemas, used by chronically constipated patients, has rarely been reported. In the largest series, Paran *et al.* reported that three of 13 patients with rectal perforation as a result of retrograde enema died because of late diagnosis.² Gayer *et al.* reported 14 elderly patients (average age 80 years) with rectal perforation as



a result of cleansing enema. Surgery was carried out in 10 of 14 patients, and nine of the 14 patients died. Interestingly, in all of these cases the enema was given by paramedic personnel.³ It is perhaps not so well known that the rectal wall, even in the absence of disease, can be perforated by the tip of a rubber catheter introduced for the purpose of administering a simple cleansing enema.⁴ Because of the possible risk of morbidity and mortality, especially in elderly patients in whom the process can be more catastrophic, rectal perforation risk should be kept in mind and administration of rectal cleansing enemas should be carried out gently and carefully by paramedic personnel. Also, the position of the body when inserting the enema tip is important. An enema should be carried out, in principle, with the patient in the left lateral decubitus position.⁵

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 \pm 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,

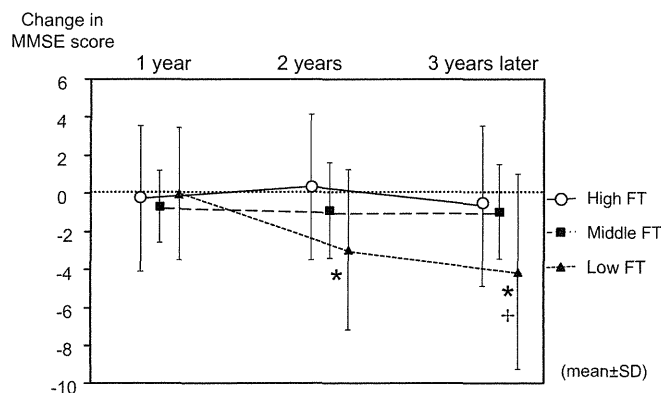


Figure 1. Change in Mini-Mental State Examination (MMSE) score according to tertile of serum free testosterone (FT) level in men. FT tertile: high, >36.1 pmol/L, $n = 17$; middle, 29.1 – 35.4 pmol/L, $n = 17$; low, <28.8 pmol/L, $n = 18$. * $P < 0.05$ vs highest FT group, + $P < 0.05$ vs middle FT group.

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.

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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REFERENCES

1. Ulubae A, Lee DM, Purandare N et al. Activation effects of sex hormones on cognition in men. *Clin Endocrinol* 2009;71:607–623.
2. Yaffe K, Lui LY, Zmuda J et al. Sex hormones and cognitive function in older men. *J Am Geriatr Soc* 2002;50:707–712.
3. Moffat SD, Zonderman AB, Metter EJ et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab* 2002;87:5001–5007.
4. Fukai S, Akishita M, Yamada S et al. Association of plasma sex hormone levels with functional decline in elderly men and women. *Geriatr Gerontol Int* 2009;9:282–289.
5. Mahoney FI, Barthel DW. Functional evaluation: Barthel Index. *Md State Med J* 1965;14:61–65.
6. Lawton MP, Brody EM. Assessment of older people, self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
7. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for clinician. *J Psychiatr Res* 1975;12:189–198.
8. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988;24:709–711.
9. Toba K, Nakai R, Akishita M et al. Vitality Index as a useful tool to assess elderly with dementia. *Geriatr Gerontol Int* 2002;2:23–29.

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 individu-

als 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 than 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 study⁵ 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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