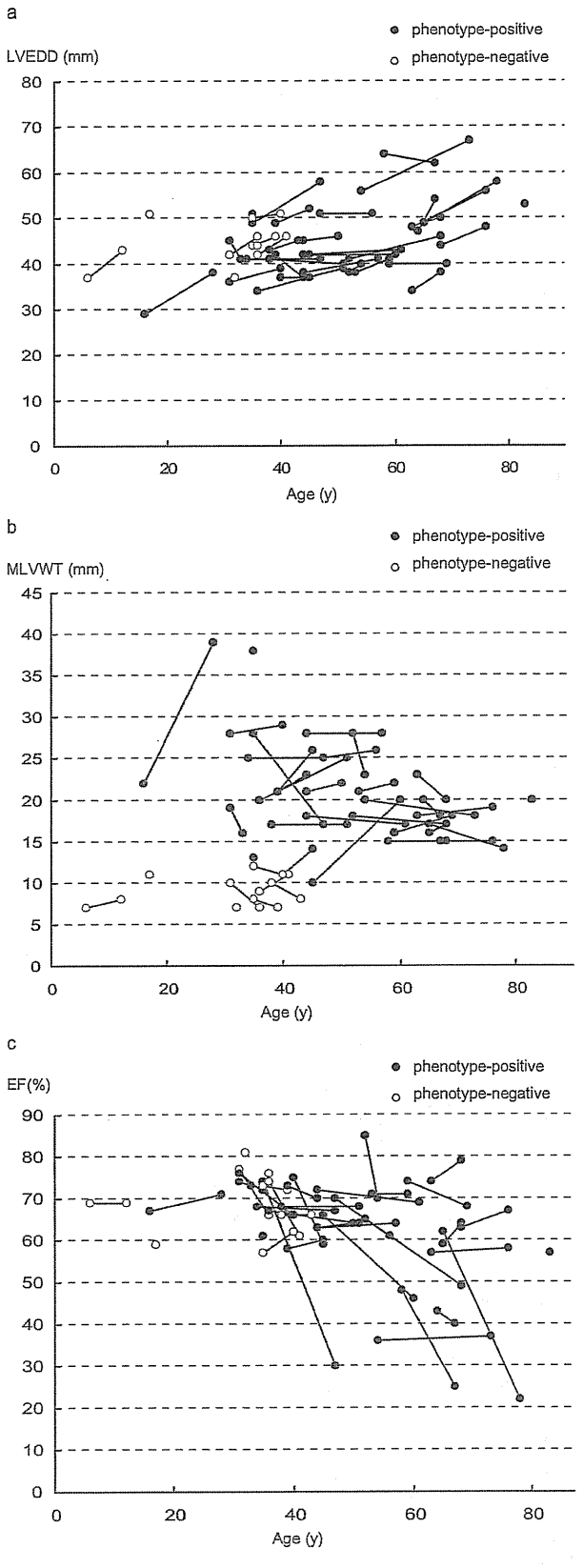

Figure 3 Longitudinal echocardiographic changes in 39 genotype-positive individuals during the follow-up period. Reproduced from Kubo *et al.*,[28] with permission from Elsevier. (a) Changes in left ventricular end-diastolic diameter (LVEDD); (b) changes in maximum left ventricular wall thickness (MLVWT); (c) changes in ejection fraction (EF).

drawn from this large genotype-phenotype correlation study is that the presence or absence of any HCM-causing mutations is closely related to ventricular and septal morphological features, irrespective of age. Sarcomere protein gene defects seem to have a predilection for a reverse curvature septal phenotype regardless of age. In the clinical situation, the shape of the LV may be useful for defining the etiology and therefore lead to prompt management.

Clinical course of HCM: lifelong LV remodeling and complications

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder and the phenotype is not a static manifestation; LVH can appear at virtually any age and increase or decrease dynamically throughout life.[27] We recently presented this concept of lifelong LV remodeling of HCM caused by a founder frame-shift deletion mutation in *MYBPC3*.[28] In that study, 39 individuals with an identical mutation (S593fs: a one-base deletion of a thymidine at nucleotide 11645) (30 patients with phenotype-positive, nine individuals with phenotype-negative) were followed up for 8.0 ± 5.4 years. Figure 3(a) shows that LV end-diastolic diameter gradually became larger with advancing age. Figure 3(b) shows that maximum LV wall thickness was thinner in elderly patients than in young patients with HCM. Reduction of ejection fraction (EF) occurred in some patients after middle age (Fig. 3c). The "dilated phase of HCM" (EF < 50%), characterized by LV systolic dysfunction and irreversible heart failure, was observed in seven of the 39 individuals. In general, the dilated phase of HCM occurs in 5–10% of patients. It is usually associated with LV remodeling with wall thinning and cavity dilatation, resembling the morphological features of dilated cardiomyopathy. On the other hand, there are other patients who may experience more gradual and subtle LV remodeling with regression in wall thickness, associated with advancing age (but not linked to systolic dysfunction or clinical deterioration). These morphological and functional changes were not specific to this mutation of *MYBPC3*, but were also seen in patients with other genetic defects.[29,30]

Figure 4 is a schema depicting a lifelong LV remodeling process and clinical complications in HCM. Sudden death occurs most commonly in children and young adults, although the risk extends across a wide

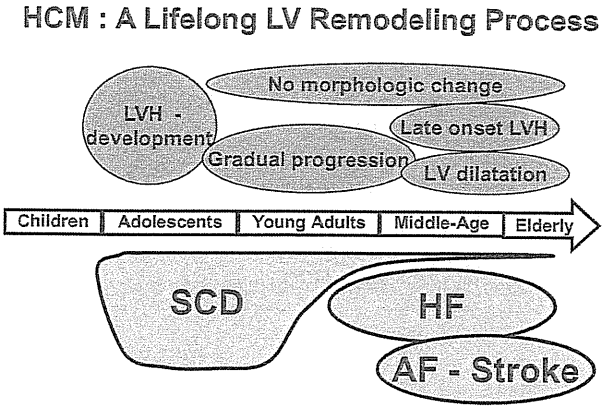

Figure 4 Diagram of a lifelong left ventricular remodeling process and clinical complications in HCM. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; HF, heart failure; LVH, left ventricular hypertrophy; SCD, sudden cardiac death.

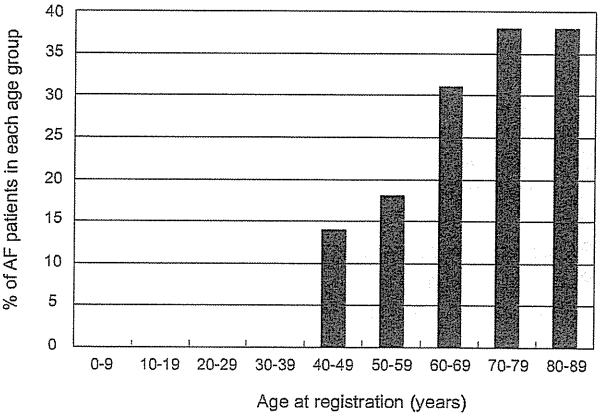

Figure 5 Prevalence of AF patients in each age group at registration from Kochi RYOMA study. AF; atrial fibrillation. Reproduced from Kubo *et al.*,[13] with permission from The Japanese Circulation Society.

age range through to mid-life and beyond.[3,31] On the other hand, heart failure and stroke occur more frequently in mid-life and beyond.[12,32] A large-scale analysis of 744 patients in a predominantly unselected cohort (USA and Italy) showed that HCM-related deaths occurred in 86 patients over a period of 8 ± 7 years and that there were three distinctive modes of deaths during different periods of life.[12] The distribution of age at deaths was as follows: (i) sudden deaths in 44 patients aged 45 ± 20 years; (ii) heart failure deaths in 31 patients aged 56 ± 19 years; and (iii) stroke deaths associated with atrial fibrillation in 11 patients aged 73 ± 14 years. Morphological and functional variations, including gradual progression or regression of hypertrophy, late onset of LVH, LV dilatation and sometimes reduced LV systolic function, and clinical complications such as sudden death, heart failure, stroke and atrial fibrillation, become more diverse in patients of middle or advanced age. Most cases of HCM present remarkable evolution of clinical features throughout life, although the severity of the phenotype and the speed of progression are different in each patient. A primary genetic defect and other modifying factors are thought to regulate this lifelong process and to determine the clinical features. It is important to manage HCM patients from the standpoint of longitudinal evolution, in order to prevent sudden and unexpected death often seen in children and young adults, and also to better manage advanced heart failure and to prevent embolic stroke in middle-aged and elderly patients.

Significance of atrial fibrillation in HCM

From the baseline characteristics at registration of the above-mentioned Kochi RYOMA study, we presented the impact of atrial fibrillation (AF) in patients with HCM, particularly significant in middle-aged or elderly patients.[13]

Seventy-four (28%) of the 261 patients with HCM at registration in the Kochi RYOMA study had documentation of paroxysmal or chronic AF. The reported prevalence of AF in several HCM populations was approximately 20%.[33–36] In our study, the prevalence of AF was 28% and this relatively high prevalence is probably due to our aged cohort. In fact, Figure 5 shows that the prevalence of AF increased with advance of age in our study.

Clinical characteristics of patients with AF at registration in comparison with those of patients without AF are shown in Table 2. Patients with AF at registration were older than those without AF. Both at diagnosis and registration, patients with AF were more symptomatic. Furthermore, at registration, most patients (93%) were in New York Heart Association (NYHA) functional class I or II irrespective of complications of AF, but 17 of the remaining 18 patients in NYHA III had AF. Thirty-seven (50%) of the 74 patients with AF suffered from morbid events (embolism and/or heart failure admission). In fact, 15 of the 19 patients with embolic events had AF prior to or at the time of embolic events. Of those 15 patients, six had first detection of AF at the time of embolism (no warfarization). Of the nine patients who had AF prior to embolic events, warfarin had been prescribed in seven patients and not been given in two patients. Severe heart failure requiring hospitalization also occurred more frequently in patients with AF. Eight of the 29 patients who had a history of heart failure admission showed LV systolic dysfunction (dilated phase of HCM), and the other 21 patients were hospitalized due to diastolic heart failure. AF occurred prior to diastolic heart failure in 20 of those 21 patients.

Table 2 Clinical characteristics of HCM patients with AF at registration

	Patients with AF ($n = 74$)	Patients without AF ($n = 187$)	P
Age at registration, years	69 ± 9	62 ± 15	<0.001
Sex: male, *n* (%)	51 (69%)	122 (65%)	0.571
Age at diagnosis, years	57 ± 13	56 ± 16	0.497
Reason for diagnosis: symptoms, *n* (%)	57 (77%)	68 (36%)	<0.001
Presence of symptoms at diagnosis, *n* (%)	60 (81%)	111 (59%)	0.001
Presence of symptoms at registration, *n* (%)	59 (80%)	106 (57%)	0.001
NYHA functional class at registration, *n* (%)			
I	26 (35%)	120 (64%)	<0.001
II	31 (42%)	66 (35%)	0.320
III and IV	17 (23%)	1 (1%)	<0.001
History of embolic complications, n (%)	15 (20%)	4 (2%)	<0.001
History of heart failure admission, n (%)	27 (36%)	2 (1%)	<0.001

Reproduced from Kubo *et al.*,[13] with permission from The Japanese Circulation Society. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association.

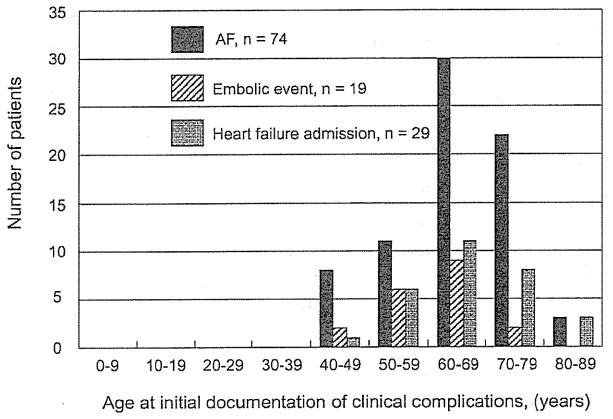

Figure 6 Age at initial documentation of clinical complications from Kochi RYOMA study. AF, atrial fibrillation. Reproduced from Kubo *et al.*,[13] with permission from The Japanese Circulation Society.

Distribution of ages at initial documentation of clinical complications is shown in Figure 6. AF, embolism and heart failure admission occurred in patients over 40 years of age. The distribution of ages of patients with these morbid events is similar to that at the time of initial documentation of AF. In our unselected regional registry, AF is the major determinant of clinical deteriorations, including hospitalization for heart failure and embolic events, in patients with HCM. Olivotto *et al.* reported that patients with AF had increased risk for HCM-related death because of excess heart failure-related mortality.[32] AF seems to be an important factor for both HCM-related mortality and HCM-related morbidity.

In the present study, clinical complications including AF, embolic events and hospitalization for heart failure were evaluated retrospectively from the baseline characteristics at registration in the Kochi RYOMA study. Further studies on outcome, prognosis and prognostic factors in patients with HCM of this cohort study as a prospectively assembled, community-based and unselected patient population are needed.

Conclusion

In an unselected regional HCM population, elderly patients were predominant despite genetic abnormalities being the cause of the disease. Cardiac hypertrophy that becomes clinically apparent late in life can be a genetic disorder, and mutations in the cardiac myosin-binding protein C gene are the most common cause of late-onset or elderly HCM. In the morphological features, sarcomere gene defects seem to have a predilection for a crescent-shaped LV cavity with reversed septal curvature even in elderly patients, different from previous reports of morphological characteristics in the elderly before gene testing became available. In the middle-aged or elderly patients, heart failure and embolic events, which were strongly associated with atrial fibrillation, in addition to sudden death were shown to be very important. It is important to manage HCM patients from the standpoint of longitudinal evolution in order to prevent those clinical complications.

Acknowledgments

We would like to thank the families and physicians who made this study possible. The study was supported by a grant from NOVARTIS Foundation for Gerontological Research.

References

1 Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997; **336**: 775–785.

2 Maron BJ, McKenna WJ, Danielson GK *et al.* American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; **42**: 1687–1713.

3 Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; **287**: 1308–1320.

4 Niimura H, Bachinski LL, Sangwatanaroj S *et al.* Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med* 1998; **338**: 1248–1257.

5 Maron BJ, Niiura H, Casey SA *et al.* Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. *J Am Coll Cardiol* 2001; **38**: 315–321.

6 McKenna WJ, Deanfield JE, Faruqui A, England D, Oakley MC, Goodwin JF. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. *Am J Cardiol* 1981; **47**: 532–538.

7 Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. *Am J Cardiol* 1981; **48**: 252–257.

8 Seiler C, Hess OM, Schoenbeck M *et al.* Long-term follow-up of medical versus surgical therapy for hypertrophic cardiomyopathy: a retrospective study. *J Am Coll Cardiol* 1991; **17**: 634–642.

9 Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. *J Am Coll Cardiol* 1995; **26**: 1529–1536.

10 Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 1999; **281**: 650–655.

11 Kofflard MJM, Ten Cate FJ, van der Lee C, van Domberg RT. Hypertrophic cardiomyopathy in a large community-based population: Clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol* 2003; **41**: 987–993.

12 Maron BJ, Olivotto I, Spirito P *et al.* Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 2000; **102**: 858–864.

13 Kubo T, Kitaoka H, Okawa M *et al.* Clinical impact of atrial fibrillation in patients with hypertrophic cardiomyopathy: results from Kochi RYOMA study. *Circ J* 2009; **73**: 1599–1605.

14 Bonne G, Carrier L, Richard P, Hainque B, Scwwartz K. Familial hypertrophic cardiomyopathy: from mutations to functional defects. *Circ Res* 1998; **83**: 580–593.

15 Ahmad F, Seidman JG, Seidman CE. The genetic basis for cardiac remodeling. *Annu Rev Genomics Hum Genet* 2005; **6**: 185–216.

16 Niimura H, Patton KK, McKenna WJ *et al.* Sarcomere protein gene mutations in hypertrophic cardiomyopathy of the elderly. *Circulation* 2002; **105**: 446–451.

17 Anan R, Niimura H, Takenaka T, Hamasaki S, Tei C. Mutations in the genes for sarcomeric proteins in Japanese patients with onset sporadic hypertrophic cardiomyopathy after age 40 years. *Am J Cardiol* 2007; **99**: 1750–1754.

18 Van Driest SL, Jaeger MA, Ommen SR *et al.* Comprehensive analysis of beta-myosin heavy chain gene in 389 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004; **44**: 602–610.

19 Van Driest SL, Vasile VC, Ommen SR *et al.* Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004; **44**: 1903–1910.

20 Maron BJ, Casey SA, Hauser RG, Appli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. *J Am Coll Cardiol* 2003; **42**: 882–888.

21 Shapiro LM. Hypertrophic cardiomyopathy in the elderly. *Br Heart J* 1990; **63**: 265–266.

22 Lever HM, Karam RF, Currie P, Healy BP. Hypertrophic cardiomyopathy in the elderly: dintinctions from the young based on cardiac shape. *Circulation* 1989; **79**: 580–589.

23 Lewis JF, Maron BJ. Elderly patients with hypertrophic cardiomyopathy: a subset with distinctive left ventricular morphology and progressive clinical course late in life. *J Am Coll Cardiol* 1989; **13**: 36–45.

24 Lewis JF, Maron BJ. Clinical and morphologic expression of hypertrophic cardiomyopathy in patients ≥65 years of age. *Am J Cardiol* 1994; **73**: 1105–1111.

25 Hirota T, Kitaoka H, Kubo T, Okawa M, Furuno T, Doi YL. Morphologic characteristics of hypertrophic cardiomyopathy of the elderly with cardiac myosin-binding protein C gene mutations. *Circ J* 2006; **70**: 875–879.

26 Binder J, Ommen SR, Gersh BJ *et al.* Echocardiography-guided genetic testing in hypertrophic cardiomyopathy: septal morphological features predict the presence of myofilament mutations. *Mayo Clin Proc* 2006; **81**: 459–467.

27 Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. *Am J Cardiol* 1998; **81**: 1339–1344.

28 Kubo T, Kitaoka H, Okawa M *et al.* Lifelong left ventricular remodeling of hypertrophic cardiomyopathy caused by a founder frameshift deletion mutation in the cardiac myosin-binding protein C gene among Japanese. *J Am Coll Cardiol* 2005; **46**: 1737–1743.

29 Kokado H, Shimizu M, Yoshio H *et al.* Clinical features of hypertrophic cardiomyopathy caused by a Lys183 deletion mutation in the cardiac troponin I gene. *Circulation* 2000; **102**: 663–669.

30 Kimura A. Molecular etiology and pathogenesis of hereditary cardiomyopathy. *Circ J* 2008; **72** (Suppl A): A38–A48.

31 Elliott PM, Poloniecki J, Dickie S *et al.* Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000; **36**: 2212–2218.

32 Kitaoka H, Kubo T, Okawa M, Hitomi N, Furuno T, Doi YL. Left ventricular remodeling of hypertrophic cardiomyopathy: longitudinal observation in a rural community. *Circ J* 2006; **70**: 1543–1549.

33 Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 1999; **281**: 650–655.

34 Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001; **104**: 2517–2524.
35 Maron BJ, Olivotto I, Bellone P *et al.* Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **39**: 301–307.
36 Nagai T, Ogimoto A, Okayama H *et al.* A985G polymorphism of the endothelin-2 gene and atrial fibrillation in patients with hypertrophic cardiomyopathy. *Circ J* 2007; **71**: 1932–1936.

Plasma Adiponectin Levels and Left Ventricular Remodeling in Hypertrophic Cardiomyopathy

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SUMMARY

Adiponectin, which is an adipose-derived protein with antiatherosclerogenic activities, has been reported to be elevated in patients with heart failure. However, there are no reports on the significance of adiponectin in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to elucidate the clinical significance of plasma adiponectin levels in HCM patients.

Clinical characteristics, echocardiographic parameters, and levels of plasma B-type natriuretic peptide (BNP) and adiponectin were evaluated in 106 HCM patients. The plasma adiponectin levels were 10.8 ± 6.3 (range, 2.7-37.3) μg/mL. Plasma adiponectin levels were positively related to age and inversely related to body mass index (BMI). Among echocardiographic parameters, % fractional shortening (r = -0.20, P = 0.03) and maximum LV wall thickness (r = -0.23, P = 0.02) were inversely related to plasma adiponectin levels. A significant correlation between plasma adiponectin levels and BNP levels was also observed (r = 0.27, P = 0.005). In multivariate analysis, BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels.

Plasma adiponectin levels are associated with impaired LV systolic function in HCM patients, but not with the LV outflow gradient. Together with BNP, adiponectin can be a useful biomarker for assessing disease severity in HCM patients. (Int Heart J 2010; 51: 51-55)

Key words: Hypertrophic cardiomyopathy, Adiponectin, B-type natriuretic peptide, LV remodeling, Heart failure

Hypertrophic cardiomyopathy (HCM), a relatively prevalent genetic cardiac disease caused by mutations in genes encoding sarcomere proteins, is clinically defined as left ventricular (LV) hypertrophy with heterogeneous clinical and morphological features in the absence of other cardiovascular diseases.[1,2] The clinical and morphological features are diverse and the natural history varies from an asymptomatic and benign clinical course to sudden premature death.[3-5]

Biomarkers are molecules that are objectively measured by laboratory techniques, which can give us useful information in patients with cardiovascular disease, including HCM.[6] Adipocytokine adiponectin is an adipose-derived protein and shows antiatherosclerogenic and insulin-sensitizing effects. The low plasma levels of adiponectin are associated with type 2 diabetes and ischemic heart disease.[7-11] Moreover, the novel cardiovascular effects of adiponectin have attracted considerable attention in patients with LV hypertrophy and chronic heart failure.[12-16] However, the significance of adiponectin has not yet been evaluated in patients with HCM. The purpose of this study was to elucidate the significance of plasma adiponectin levels in HCM.

METHODS

Patients and study protocol: The study group included 106 patients with HCM diagnosed based on echocardiographic demonstration of a hypertrophied left ventricle (maximum wall thickness ≥ 15 mm) in the absence of systemic hypertension or other cardiac disease that could produce the magnitude of evident hypertrophy. Clinical characteristics, and electrocardiographic, echocardiographic and laboratory findings were determined for all patients during a clinically stable period. Patients with renal failure (serum creatinine ≥ 2.0 mg/dL), myocardial infarction or malignancy were excluded from the study. The study protocol was approved by the Ethics Committee on Medical Research at our institute and written informed consent was provided by all patients.

Echocardiography: Echocardiographic studies were performed using a Sequoia 512 (Mountain View, CA, USA). The dimensions of the left ventricle and the left atrium were measured and the magnitude and distribution of LV hypertrophy were assessed from two-dimensional images. The greatest wall thickness measured at any site in the left ventricle was regarded as the maximum thickness. The LV outflow pressure gradient was also measured using a continuous-wave Doppler under basal conditions.

Based on echocardiographic findings, the morphologic

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subtype of HCM was defined as 1) *obstructive* (LV outflow gradient of ≥ 30 mmHg), 2) *nonobstructive*, 3) *apical* (LV wall thickening confined to the most distal region at the apex below the papillary muscle level), and 4) *dilated phase* (LV systolic impairment defined as % fractional shortening of < 25%).

Moreover, 79 patients with preserved LV systolic function were studied by tissue Doppler imaging (TDI) to evaluate the relationship between plasma adiponectin levels and diastolic function. The peak velocity of early (E) and late (A) waves and the E/A ratio were determined from transmitral flow velocity using an apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets during diastole. Tissue Doppler velocity was measured during early diastole (Ea) at the septal and lateral corners of the mitral annulus from the apical 4-chamber view by positioning the sample volume at the lateral margin of the mitral annulus. Finally, the septal and lateral E/Ea ratio was also calculated.[17]

Laboratory measurements: Peripheral venous blood samples were collected from the antecubital vein after the patients had remained supine for at least 15 minutes without discontinuing drugs. The plasma adiponectin level was measured using a sandwich enzyme-linked immunosorbent assay system (adiponectin ELISA kit, Otsuka Pharmaceutical Co., Japan). In addition, the plasma BNP level was also measured using an enzyme immunoassay (TOSOH II(BNP), TOSOH Co., Japan).

Statistical analysis: Data are presented as the mean ± SD. The nonparametric Wilcoxon rank-sum test was used to compare plasma adiponectin levels between two groups. Variables with non-normal distribution were transformed logarithmically. Correlations between plasma adiponectin levels and other variables were evaluated using univariate linear regression analysis. By forward stepwise multiple regression analysis, parameters that were associated with plasma adiponectin at the level of $P < 0.10$ on univariate analysis were analyzed. Analysis of variance (ANOVA) was used for comparison between groups and the significances of individual differences were evaluated by Tukey's HSD procedure if ANOVA was significant. A level of $P < 0.05$ was considered to indicate statistical significance.

Table I. Relationship Between Plasma Adiponectin Level and Echocardiographic Variables in All Patients

Variable	Mean ± SD	*r*	*P*
LV end-diastolic dimension (mm)	46 ± 6	0.07	0.47
LV end-systolic dimension (mm)	27 ± 7	0.20	0.04
%fractional shortening (%)	41 ± 8	-0.20	0.03
Left atrial dimension (mm)	45 ± 7	0.10	0.28
Maximum LV wall thickness (mm)	20 ± 4	-0.23	0.02

SD indicates standard deviation; and LV, left ventricular.

Results

Patient characteristics: The patients were aged 63 ± 13 years and 69 (65%) were male. Body mass index (BMI) was 24.2 ± 2.8 kg/m^2 and 43 patients (41%) had a BMI of > 25 kg/m^2. Most of the patients had no or mild symptoms and 7 (7%) had symptoms of severe heart failure (New York Heart Association functional class III). Thirty-six patients (34%) had a family history of HCM. Patients had the following HCM subtypes: obstructive (n = 10), nonobstructive (non-apical) (n = 67), apical (n = 24), and dilated phase (n = 5). Of these 106 patients, 47 were administered beta-blockers and 35 were taking calcium antagonists. In addition, 30 patients were taking either angiotensin converting enzyme inhibitors or angiotensin receptor blockers for mild systemic hypertension or heart failure due to LV systolic impairment. None had been prescribed PPAR-γ agonists.

Adiponectin levels and clinical characteristics: The mean plasma adiponectin level of the patients was 10.8 ± 6.3 (range, 2.7-37.7) μg/mL. The mean adiponectin level in females was higher than that in males (13.1 ± 6.9 μg/mL versus 9.6 ± 5.6 μg/mL, P = 0.002). Plasma adiponectin levels were positively related to age (r = 0.22, P = 0.02) and inversely related to BMI (r = -0.27, P = 0.004). Nineteen patients with atrial fibrillation showed higher plasma adiponectin levels compared to those with sinus rhythm (14.6 ± 9.2 μg/mL versus 10.0 ± 5.2 μg/mL, P = 0.03). The

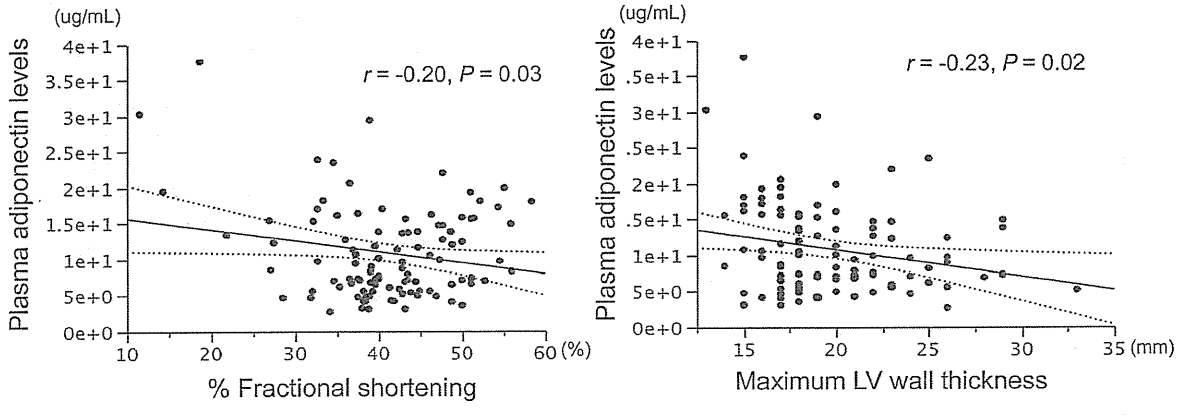

Figure 1. Relationship between plasma adiponectin levels and echocardiographic parameters such as % fractional shortening and maximum left ventricular (LV) wall thickness. The dotted lines represent the 95% confidence limit for the fitted line.

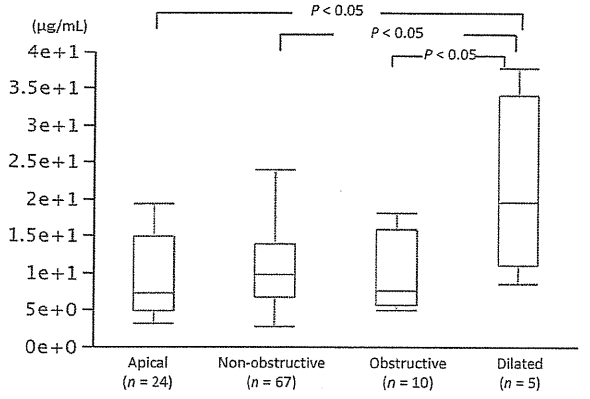

Figure 2. Comparison of plasma adiponectin levels in subtypes of hypertrophic cardiomyopathy. Adiponectin levels were higher in dilated HCM than in other subtypes of HCM.

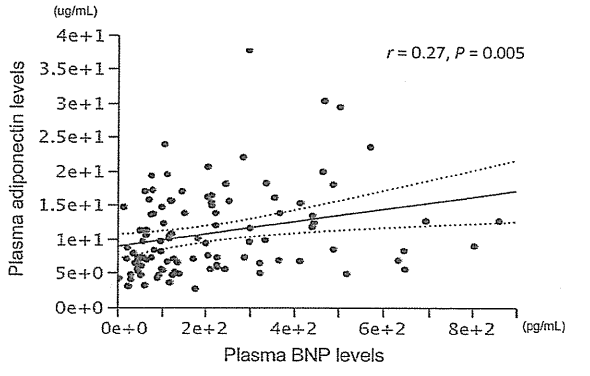

Figure 3. Relationship between plasma adiponectin levels and BNP levels. The dotted lines represent the 95% confidence limit for the fitted line.

plasma adiponectin levels in 7 patients with severe heart failure symptoms were slightly higher than those in patients with no or mild symptoms (13.8 ± 8.6 μg/mL versus 10.6 ± 6.1 μg/mL, P = NS). The plasma adiponectin levels did not differ according to the drug administered, including beta-blockers, calcium antagonists, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Adiponectin levels and echocardiographic findings: Table I shows the relationship between the plasma adiponectin levels and echocardiographic parameters in all patients. The plasma adiponectin levels were positively related to LV end-systolic dimension, and inversely related to % fractional shortening and maximum LV wall thickness (Figure 1). The plasma adiponectin levels in obstructive HCM did not differ from that in other subtypes of HCM (10.9 ± 6.3 μg/mL versus 10.0 ± 5.2 μg/mL, P = NS). As a consequence, plasma adiponectin levels in patients with dilated HCM were significantly higher than those in patients with other HCM subtypes (Figure 2).

Relation between plasma levels of adiponectin l and BNP: The mean plasma BNP level was 211 ± 187 (range, 4-861) pg/mL. Plasma BNP levels were positively related to plasma adiponectin levels (Figure 3).

Multivariate analysis: Forward stepwise multiple regression analysis showed that BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels (Table II).

Diastolic dysfunction and plasma adiponectin levels in patients with preserved LV systolic function: There were no significant correlations between plasma adiponectin levels and conventional echocardiographic parameters in patients with preserved LV systolic function. Plasma adiponectin levels were significantly related to septal E/Ea ratio (r = 0.24, P = 0.03) and plasma BNP levels (r = 0.25, P = 0.01). However, by multivariate analysis, septal E/Ea was not an independent predictor of plasma adiponectin levels (Table III).

Table II. Stepwise Multiple Regression Analysis in All Patients

Variable	F	P
Age	1.39	0.24
Gender (male 1)	3.05	0.08
BMI	8.95	0.003
% Fractional shortening	6.04	0.01
Maximum LV wall thickness	3.27	0.07
Plasma BNP levels	8.14	0.005

BMI indicates body mass index; and BNP, B-type natriuretic peptide.

Table III. Stepwise Multiple Regression Analysis in Patients With Preserved LV Systolic Function

Variable	F	P
Age	6.04	0.16
Gender (male 1)	2.98	0.08
BMI	3.23	0.07
Septal E/Ea	1.14	0.29
Plasma BNP levels	3.26	0.08

LV indicates left ventricular; BMI, body mass index; E, peak velocity of early (E) waves determined from transmitral flow velocity; Ea, early diastole velocity at the corners of the mitral annulus by tissue Doppler imaging; and BNP, B-type natriuretic peptide.

Discussion

To the best of our knowledge, this is the first report to describe the significance of plasma adiponectin in patients with HCM. The main finding of this study is that the levels of plasma adiponectin were related to LV systolic impairment due to LV remodeling in patients with HCM.

Adiponectin and LV systolic impairment: Measurement of biomarkers such as neurohormones, inflammatory biomarkers, and metabolic biomarkers can help in understanding the pathophysiology of cardiovascular disease.[18] For example, circulating levels of BNP constitute an established predictor of outcome in patients with chronic heart failure

associated with acquired cardiac disease. Recently, metabolic biomarkers have gained attention in various cardiovascular diseases. Adiponectin is an antiatherosclerogenic and insulin-sensitizing protein comprising 247 amino acids produced by white adipose tissue. It is abundant in circulating plasma, with concentrations between 5-10 μg/mL in humans. Adiponectin is related to type 2 diabetes, essential hypertension, and ischemic heart disease.[7-11,16] Interestingly, several investigators have recently found elevated plasma adiponectin levels in patients with heart failure, and have suggested that it might be a prognostic predictor.[12-14] Tsutamoto and colleagues identified elevated plasma adiponectin levels in patients with chronic heart failure and found that it was an independent prognostic predictor.[14] Although the precise mechanism of elevation of adiponectin is unclear in patients with heart failure, the following explanations can be considered.[19,20] Firstly, progression to severe heart failure is often associated with weight loss, which results in an increase in the plasma adiponectin level. Secondly, mRNA and protein expression of the adiponectin receptor adipoR1 is increased in the left ventricle of the infarcted, compared with the normal mouse heart. Moreover, adiponectin-knockout mice develop exacerbated LV dilatation, myocyte hypertrophy, and contractile dysfunction after myocardial infarction compared with wild-type mice.[21] Therefore, adiponectin might protect the heart from LV remodeling, although it is unclear whether or not high adiponectin levels are a compensatory mechanism.

The clinical and pathological characteristics of HCM involve a number of diverse mechanisms. Therefore, measurement of biomarkers may be useful to assess the pathophysiology, disease severity, and prognosis in HCM. For example, it has been reported that plasma BNP and N-terminal proBNP levels are related to heart failure symptoms and might be related to prognosis in patients with HCM.[22,23] Plasma BNP levels are affected by several factors such as LV outflow tract gradient, LV wall thickness, LV diastolic function, and LV systolic impairment.[24,25]

However, there are no reports on the significance of adiponectin in HCM. We found here that the plasma adiponectin levels were not affected by the LV outflow gradient and were independently related to LV systolic impairment due to LV remodeling. A significant proportion (5-10%) of patients with HCM progress to LV systolic impairment due to LV remodeling (so called dilated HCM or end-stage HCM).[26-28] To recognize this clinical entity is important because this subgroup of patients develops refractory heart failure and has a poor prognosis. A precise explanation for the relationship between LV systolic impairment and high plasma adiponectin levels in HCM is difficult in our study. However, a recent report showed the natriuretic peptides (atrial natriuretic peptide and BNP) enhance adiponectin production by human adipocytes both *in vivo* and in patients with heart failure.[29] As we have shown, plasma adiponectin levels were related to plasma BNP levels in this study. Therefore, plasma adiponectin levels might be partially regulated by plasma BNP levels also in patients with HCM.

In conclusion, plasma adiponectin levels can be a useful marker, particularly with other biomarkers such as BNP, for assessing disease severity such as a decline in LV systolic function in patients with HCM.

Study limitations: Several limitations are associated with this study. Firstly, the adiponectin level was measured only at one point. Secondly, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were prescribed for some patients due to mild systemic hypertension or LV systolic dysfunction. Previous studies have shown that angiotensin converting enzyme inhibitors or angiotensin receptor blockers increased the plasma adiponectin levels and the effect of beta-blockers is controversial.[30-31] Therefore, it could not be ruled out that plasma adiponectin levels were influenced by the medication, although we did not identify any statistically significant relationship between them.

Adiponectin has been reported to modulate hypertrophic signals and be related to diastolic function in patients with hypertension.[15,16] Therefore, it would be interesting to determine whether plasma adiponectin levels affect the degree of LV hypertrophy, LV mass, and LV diastolic function in patients with HCM. In this study using echocardiography, plasma adiponectin levels were inversely related to maximum LV thickness in all patients, but were not related to LV wall thickness in patients with preserved LV systolic function. Moreover, plasma adiponectin levels were not related to diastolic dysfunction assessed by TDI by multivariate analysis, although it was weakly related to septal E/Ea by univariate analysis. However, echocardiography including TDI is limited to assess LV mass and LV diastolic function in HCM.[32] Cardiac magnetic resonance is a useful tool with which to assess LV mass and myocardial fibrosis in HCM.[33,34] Therefore, further investigations are warranted to elucidate the significance and mechanisms of adiponectin for LV hypertrophy and diastolic dysfunction in patients with HCM.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002; 287: 1308-20. (Review)
2. Elliot P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004; 363: 1881-91.
3. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995; 26: 1699-708.
4. Maron BJ, Olivotto I, Spirito P, *et al.* Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000; 102: 858-64.
5. Cecchi F, Olivotto I, Betocchi S, *et al.* The Italian Registry for hypertrophic cardiomyopathy: a nationwide survey. Am Heart J 2005; 150: 947-54.
6. Cambronero F, Marín F, Roldán V, Hernández-Romerp D, Valdés M, Lip GY. Biomarkers of pathophysiology in hypertrophic cardiomyopathy: implications for clinical management and prognosis. Eur Heart J 2009; 30: 139-51. (Review)
7. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions, J Am Coll Cardiol 2007; 49: 531-8. (Review)
8. Kumada M, Kihara S, Sumitsuji S, *et al.* Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003; 23: 85-9.
9. Hotta K, Funahashi T, Arita Y, *et al.* Plasma concentration of a

novel adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20: 1595-9.
10. Hotta K, Funahashi T, Bodkin NL, *et al.* Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001; 50: 1126-33.
11. Lindsay RS, Funahashi T, Hanson RL, *et al.* Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360: 57-8.
12. Kistorp C, Faber J, Galatius S, *et al.* Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005; 112: 1756-62.
13. George J, Patal S, Wexler D, *et al.* Circulating adiponectin concentrations in patients with congestive heart failure. Heart 2006; 92: 1420-4.
14. Tsutamoto T, Tanaka T, Sakai H, *et al.* Total and high molecular weight adiponectin, hemodynamics, and mortality in patients with chronic heart failure. Eur Heart J 2007; 28: 1723-30.
15. Shibata R, Ouchi N, Ito M, *et al.* Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med 2004; 10: 1384-9.
16. Hong SJ, Park CG, Seo HS, Oh DJ, Ro YM. Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index. Blood Press 2004; 13: 236-42.
17. Sohn D, Chai I, Lee DJ, *et al.* Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474-80.
18. Tang WH, Francis GS, Morrow D, *et al.* National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007; 116: e99-109.
19. Kintscher U. Does adiponectin resistance exist in chronic heart failure? Eur Heart J 2007; 28: 1676-7.
20. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007; 73: 298-309. (Review)
21. Shibata R, Izumiya Y, Sato K, *et al.* Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol 2007; 42: 1065-74.
22. Maron BJ, Tholakanahalli VN, Zenovich AG, *et al.* Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. Circulation 2004; 109: 984-9.
23. Mutlu B, Bayrak F, Kahveci G, Degertekin M, Eroglu E, Basaran Y. Usefulness of N-terminal pro-B-type natriuretic peptide to predict clinical course in patients with hypertrophic cardiomyopathy. Am J Cardiol 2006; 98: 1504-6.
24. Nishigaki K, Tomita M, Kagawa K, *et al.* Marked expression of plasma brain natriuretic peptide is a special feature of hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 1996; 28: 1234-42.
25. Briguori C, Betocchi S, Manganelli F, *et al.* Determinants and clinical significance of natriuretic peptides in hypertrophic cardiomyopathy. Eur Heart J 2001; 22: 1328-36.
26. Thaman R, Gimeno JR, Murphy RT, *et al.* Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart 2005; 91: 920-5.
27. Harris KM, Spirito P, Maron MS, *et al.* Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006; 114: 216-25.
28. Kitaoka H, Kubo T, Okawa M, Hitomi N, Furuno T, Doi YL. Left ventricular remodeling of hypertrophic cardiomyopathy: longitudinal observation in rural community. Circ J 2006; 70: 1543-9.
29. Tsukamoto O, Fujita M, Kato M, *et al.* Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. J Am Coll Cardiol 2009; 53: 2070-7.
30. Furuhashi M, Ura N, Higashiura K, *et al.* Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 2003; 42: 76-81.
31. Yamaji M, Tsutamoto T, Tanaka T, *et al.* Effect of carvedilol on plasma adiponectin concentration in patients with chronic heart failure. Cir J 2009; 73: 1067-73.
32. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation 2007; 116: 2702-8.
33. Olivotto I, Maron MS, Autore C, *et al.* Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008; 52: 559-66.
34. Nagueh SF, Mahmarian JJ. Noninvasive cardiac imaging in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2006; 48: 2410-22. (Review)

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

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 2011; 11: 196–203.**

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

Table 2 Association between potential confounding variables and DHEA-S tertiles in women

Characteristic	DHEA-S tertiles T1 <1.17 μmol/L (<43 μg/dL), $n = 33$	T2 1.17–1.49 μmol/L (43–55 μg/dL), $n = 32$	T3 >1.49 μnmol/L (>55 μg/dL), $n = 32$	*P*-value
Age, years	83 ± 6	82 ± 6	80 ± 6	0.08
Nutritional parameters				
Body mass index, kg/m^2	22.3 ± 2.7	22.5 ± 3.2	23.7 ± 2.7	0.31
Hemoglobin, g/dL	12.6 ± 1.4	12.6 ± 1.2	13.1 ± 1.1	0.16
Albumin, g/dL	4.1 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	0.18
Total cholesterol, mg/dL	205 ± 30	204 ± 35	205 ± 35	0.99
Prevalent diseases, *n* (%)				
Hypertension	10 (30)	14 (44)	15 (47)	0.47
Heart disease	4 (12)	7 (22)	8 (25)	0.46
Stroke	5 (15)	4 (13)	6 (19)	0.79
Diabetes mellitus	5 (15)	4 (13)	5 (16)	0.90
Osteoarthropathy	8 (24)	11 (34)	13 (40)	0.47
Lung disease	3 (9)	2 (6)	2 (6)	0.56
Other chronic diseases	17 (52)	19 (59)	18 (56)	0.90
Functional parameters				
Barthel Index	90 ± 7	93 ± 8	95 ± 8	0.04
HDS-R	23 ± 6	22 ± 7	25 ± 5	0.39
Vitality Index	9.2 ± 1.4	9.1 ± 2.2	8.8 ± 2.9	0.35
GDS	6.8 ± 2.6	5.9 ± 3.4	6.9 ± 3.3	0.16
Sex hormone levels				
DHEA-S, μmol/L	0.8 ± 0.2	1.3 ± 0.1	2.0 ± 0.3	<0.01
(μg/dL)	30 ± 7	49 ± 4	73 ± 12	
Testosterone, nmol/L	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	0.81
(ng/dL)	35 ± 17	36 ± 17	37 ± 13	
Estradiol, pmol/L	56 ± 32	57 ± 37	67 ± 46	0.41
(pg/mL)	15.3 ± 8.6	15.5 ± 10.2	18.3 ± 12.5	

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.

circulatory system (HR = 13.1, 95% CI = 2.39–72.3, $P < 0.01$), while there was no association with deaths from non-circulatory causes (HR = 0.93, 95% CI = 0.86–1.02, $P = 0.14$).

Discussion

In this small prospective study of Japanese elderly who were receiving care in facilities, a low testosterone level was associated with mortality in men independent of multiple risk factors and pre-existing health conditions. In addition, a low DHEA-S level in older women was related to increased mortality. In contrast, DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Recent prospective cohort studies in Western countries have yielded inconsistent findings about the use of a low total testosterone level as a predictor of all-cause and cardiovascular mortality in middle-aged to older men.[4,5,38,39] In the two studies that found no significant prediction of mortality,[38,39] the populations were younger (mean or median ages were in the early 50s), testosterone levels were higher and mortality rates were lower (11.6 and 15.4/1000 person-years, respectively) compared to those in studies that found positive results. In the present study, although the sample size was small, the subjects were frail and older than those in any previously reported studies, with a relatively small age range and higher mortality rate. Therefore, the relation between testosterone level and mortality might have been easier to detect in our study than in other studies with healthy middle-aged and older men.

There could be several mechanisms by which endogenous testosterone affects mortality in men. Although the number of subjects was too small to perform cause-specific analysis in the present study, other studies have reported that a low testosterone level predicted increased risk of death due to CVD.[4,5] Further, in addition to the relation to muscle strength, physical performance and ADL,[10–12,21] some but not all reports have

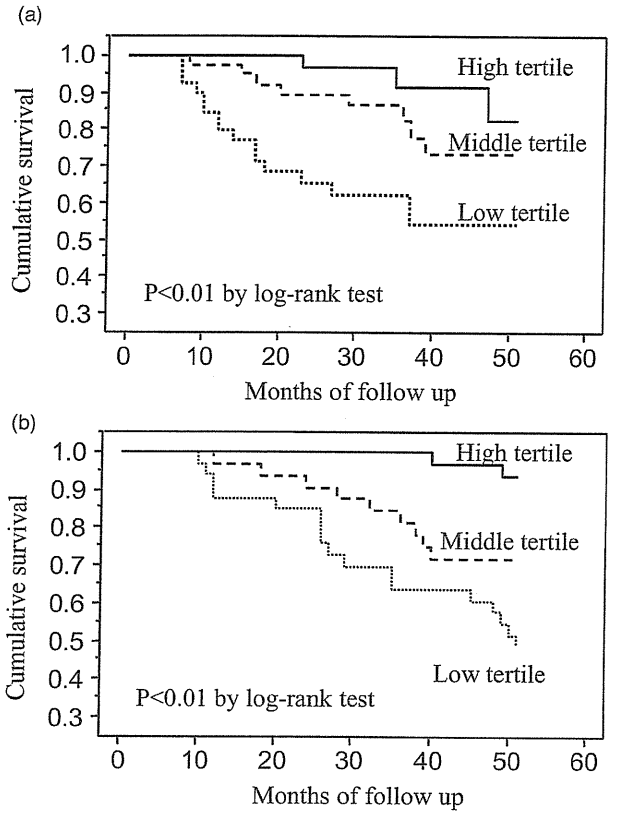

Figure 1 (a) Survival curves by tertile group of plasma testosterone level in men. (b) Survival curves by tertile group of plasma dehydroepiandrosterone sulfate level in women.

demonstrated an association between low testosterone level in older men and risk of a fall or fracture and frailty.[12–14,20] It is noteworthy that in the 10 men who died of respiratory infection, four had a history of a fall and fracture, which resulted in worse disability. Accordingly, a low testosterone level may contribute to frailty, which influences men's susceptibility to illness and falls and the capability to recover from disease or fractures, and thereby affects mortality.

Other than aging, systemic illness can result in decreased testosterone levels; therefore, low testosterone levels in older men could be attributable to acute and chronic diseases,[40] and the possible reverse causality should be considered. To evaluate this possibility, we excluded the first 12 months of observation and still found that in 12–52 months of observation, men in the low testosterone tertile had a greater risk of mortality from all causes than those in higher tertiles. We carefully excluded subjects with critical diseases and conditions at baseline, although our subjects were old with multiple chronic diseases, and it is difficult to exclude the possibility that men with subclinical critical conditions might have been included. Moreover, at baseline, there was a significant difference in functional status (ADL and cognition) and nutritional parameters (serum albumin and hemoglobin levels) between testosterone tertiles, as reported previously;[21] thus, our results need to be confirmed in a cohort with no difference in these factors between testosterone groups to exclude the influence of these biases on mortality. Also, it needs to be explored whether low testosterone in older men plays a pathogenic role, such as affecting the immune system, developing physical frailty and depression, or simply serves as a marker for biological vulnerability and poor prognosis. Long-term studies also need to test whether testosterone treatment should yield clinically significant improvements in mortality in appropriately selected older men, with consistent symptoms and signs and unequivocally low serum testosterone levels.

Low DHEA-S has been associated with increased all-cause and cardiovascular mortality in older men;[26,27,41] however, no association was found in the present study. Because DHEA(-S) is an inactive prohormone and we and others have found an association between testosterone and mortality,[3–8] it is suggested that testosterone could be a stronger predictor of mortality in older men.

On the other hand, a low DHEA-S level in older women was associated with a poor prognosis after adjusting for multiple factors related to mortality. Other previous reports showed an inconsistent relationship between DHEA-S level and mortality in older women,[29–31] possibly due to differences in the cohorts including age, DHEA-S level, heterogeneity of health status and mortality rate, and the method of statistical analysis used to demonstrate the relationship, regression models with linear/non-linear assumption.

Previous studies support a potential physiological role of DHEA-S, which could contribute to reduced mortality, an anti-inflammatory action and immune regulatory activity.[42] However, there are still many unanswered questions regarding DHEA's role in aging, and there is insufficient evidence to support DHEA replacement for increasing longevity in older women. It also needs to be explored whether the DHEA-S level contributes to mortality or is merely a biomarker of the underlying health condition of older women.

Our study has some limitations. First, the sample size was too small to reach a clear conclusion with strong statistical power, thus limiting the precision of the estimates, which is reflected in the broad range of HR for mortality. Second, the results are based on single measurements of sex hormones, which do not allow assessment of changes in levels over time; therefore, they may overestimate or underestimate the association between hormone levels and mortality. Third, we did not measure estradiol levels in men, although it would have been helpful to see whether the effects of testosterone on mortality are mediated by testosterone itself or by aromatization to estradiol in older men. Finally, active forms of testosterone such as bioavailable and

Table 3 Hazard ratios for low tertile 1 vs tertiles 2–3 of plasma sex hormone levels for all-cause mortality in men and women

	Unadjusted	Model 1	Model 2
Men (n = 117)			
HR of low testosterone for mortality	3.83 (1.74–8.40)**	3.71 (1.54–8.04)**	3.27 (1.24–12.91)*
Excluding first-year deaths (n = 108)	3.81 (1.53–6.93)**	3.49 (1.14–7.39)**	3.08 (1.11–13.62)*
Excluding deaths from cancer (n = 113)	4.18 (1.77–9.86)**	4.03 (1.70–9.58)**	5.02 (1.51–15.41)*
Women (N = 97)			
HR of low DHEA-S for mortality	3.77 (1.77–8.07)**	3.86 (1.79–8.32)**	4.42 (1.51–12.90)*
Excluding first-year deaths (n = 95)	3.38 (1.55–7.37)**	3.43 (1.56–9.54)**	3.58 (1.12–11.46)*
Excluding deaths from cancer (n = 92)	3.82 (1.69–8.60)**	3.55 (1.54–8.19)**	3.92 (1.28–11.98)*

*P < 0.05; **P < 0.01 vs reference group (tertile 2–3). Values are expressed as HR (95% CI). Model 1, adjusted for age; Model 2, adjusted for age, nutritional parameters, functional parameters and prevalent disease. DHEA-S, dehydroepiandrosterone sulfate; HR, hazards ratio.

calculated free testosterone were not measured, because a direct assay of bioavailable testosterone or an assay of sex hormone binding globulin, which is necessary for free testosterone calculation, is not available in Japan. However, because most of the above-mentioned previous reports have shown an association of total testosterone with mortality, the fundamental findings might not have differed if active forms of testosterone had been analyzed.

In conclusion, a low testosterone level in men and a low DHEA-S level in women are associated with increased mortality risk, independent of multiple risk factors and several pre-existing health conditions in disabled elderly. To our knowledge, the present study is the first that showed testosterone as a predictor of mortality in Asian men. Also, this is the first study that investigated frail or disabled older persons receiving care at facilities. Our results imply the clinical importance of measuring plasma androgen levels even in disabled elderly to estimate their prognosis.

Acknowledgments

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References

1 UN. World population prospects: the 2008 revision. [Cited 1 Mar 2010.] Available from URL: http://www.un.org/esa/population/
2 Statistics and Information Department Minister's Secretariat Ministry of Health, Labour and Welfare Japanese Government. Abridged life tables for Japan. 2008 Ministry of Health, Labour and Welfare. [Cited 1 Mar 2010.] Available from URL: http://www.mhlw.go.jp
3 Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med* 2006; **166**: 1660–1665.
4 Khaw KT, Dowsett M, Folkerd E *et al.* Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 2007; **116**: 2694–2701.
5 Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008; **93**: 68–75.
6 Shores MM, Moceri VM, Gruenewald DA, Brodkin KI, Matsumoto AM, Kivlahan DR. Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in geriatric rehabilitation unit. *J Am Geriatr Soc* 2004; **52**: 2077–2081.
7 Tivesten A, Vandenput L, Labrie F *et al.* Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab* 2009; **94**: 2482–2488.
8 Vikan T, Schirmer H, Njølstad I, Svartberg J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromsø Study. *Eur J Endocrinol* 2009; **161**: 435–442.
9 Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT. Endogenous sex hormones in men aged 40–80 years. *Eur J Endocrinol* 2003; **149**: 583–589.
10 Schaap LA, Pluijm SM, Smit JH *et al.* The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. *J Clin Endocrinol* 2005; **63**: 152–160.
11 O'Donnell AB, Travison TG, Harris SS, Tenover JL, McKinlay JB. Testosterone, dehydroepiandrosterone, and physical performance in older men: results from the Massachussetts Male Aging Study. *J Clin Endocrinol Metab* 2006; **91**: 425–431.
12 Orwoll E, Lambert LC, Marshall LM *et al.* Endogenous testosterone levels, physical performance, and fall risk in older men. *Arch Intern Med* 2006; **166**: 2124–2131.
13 Fink HA, Ewing SK, Ensrud KE *et al.* Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab* 2006; **91**: 3908–3915.

14 Meier C, Nguyen TV, Handelsman DJ *et al.* Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. *Arch Intern Med* 2008; **168**: 47–54.
15 Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L. Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. *Arch Gen Psychiatry* 2008; **65**: 283–289.
16 Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. *J Am Geriatr Soc* 2002; **50**: 707–712.
17 Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab* 2002; **87**: 5001–5007.
18 Yeap BB, Beilin J, Shi Z *et al.* Serum testosterone levels correlate with haemoglobin in middle-aged and older men. *Intern Med J* 2009; **39**: 532–538.
19 Ferrucci L, Maggio M, Bandinelli S *et al.* Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med* 2006; **166**: 1380–1388.
20 Cawthon PM, Ensrud KE, Laughlin GA *et al.* Osteoporotic Fractures in Men (MrOS) Research Group. Sex hormones and frailty in older men: the osteoporotic fractures in men (MrOS) study. *J Clin Endocrinol Metab* 2009; **94**: 3806–3815.
21 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.
22 Labrie F. Adrenal androgens and intracrinology. *Semin Reprod Med* 2004; **22**: 299–309.
23 Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154**: 1–11.
24 Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ. Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *J Clin Endocrinol Metab* 2008; **93**: 801–808.
25 Barrett-Connor E, von Mühlen D, Laughlin GA, Kripke A. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. *J Am Geriatr Soc* 1999; **47**: 685–691.
26 Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. *J Bone Miner Res* 1997; **12**: 1833–1843.
27 Voznesensky M, Walsh S, Dauser D, Brindisi J, Kenny AM. The association between dehydroepiandosterone and frailty in older men and women. *Age Ageing* 2009; **38**: 401–406.
28 Cappola AR, Xue QL, Walston JD *et al.* DHEAS levels and mortality in disabled older women: the Women's Health and Aging Study I. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 957–962.
29 Glei DA, Goldman N. Dehydroepiandrosterone sulfate (DHEAS) and risk for mortality among older Taiwanese. *Ann Epidemiol* 2006; **16**: 510–515.
30 Mazat L, Lafont S, Berr C *et al.* Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proc Natl Acad Sci U S A* 2001; **98**: 8145–8150.
31 Trivedi DP, Khaw KT. Dehydroepiandrosterone sulfate and mortality in elderly men and women. *J Clin Endocrinol Metab* 2001; **86**: 4171–4177.
32 Cappola AR, O'Meara ES, Guo W, Bartz TM, Fried LP, Newman AB. Trajectories of dehydroepiandrosterone sulfate predict mortality in older adults: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci* 2009; **64**: 1268–1274.
33 Mahoney FI, Barthel DW. Functional evaluation: Barthel Index. *Md State Med J* 1965; **14**: 61–65.
34 Kato S, Shimogaki M, Onodera H *et al.* Revised Hasegawa Dementia Scale (HDS-R). *Jpn J Geriatr Psychiatr* 1991; **2**: 1339–1347.
35 Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988; **24**: 709–711.
36 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.
37 World Health Organization. *International Statistical Classification of Diseases*, 10th Revision (ICD-10). Geneva, Switzerland: World Health Organization, Version for 2007.
38 Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation* 2005; **112**: 332–340.
39 Araujo AB, Kupelian V, Page ST, Handelsman DJ, Bremner WJ, McKinlay JB. Sex steroids and all-cause and cause-specific mortality in men. *Arch Intern Med* 2007; **167**: 1252–1260.
40 Matsumoto AM. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol A Biol Sci Med Sci* 2002; **57A**: M76–M99.
41 Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. *N Engl J Med* 1986; **315**: 1519–1524.
42 Dillon JS. Dehydroepiandrosterone, dehydroepiandrosterone sulfate and related steroids: their role in inflammatory, allergic and immunological disorders. *Curr Drug Targets Inflamm Allergy* 2005; **4**: 377–385.

Geriatr Gerontol Int 2011; 11: 438–444

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.