strength were not observed. These results indicate that exercise alone is insufficient for recovery in sarcopenic elderly women.

Previous studies have indicated that declines in muscle mass are related to declines in muscle protein synthesis rates in older adults and that leucine-enriched essential amino acid mixtures are primarily responsible for the amino acid-induced muscle protein anabolism in elderly people.[11,22] These studies investigated the effects of different amino acid dosages (from 6.7 to 20.0 g/d) on protein synthesis, and the 6.0-g/d dosage provided in this study is lower than in previous studies, but the mean weights of the subjects in such studies were from 71.0 to 81.3 kg, making the dosage of amino acid between 0.090 and 0.246 g/kg of body weight. The amino acid dosage in the current study was 0.151 g/kg, which is comparable with the amounts found in the literature.[11,22,26] The results of the current study showed that muscle mass, appendicular muscle mass, and leg muscle mass significantly increased in the AAS group, which is consistent with previous findings.

Many studies have demonstrated an increase in muscle mass from nutritional supplementation, but an increase in muscle strength does not always accompany an increase in muscle mass. A recent study concluded that essential AAS alone was not sufficient to increase muscle strength.[26] Similarly, although the results of the current study showed that AAS alone increased muscle mass, improvement in muscle strength was not observed. The results of the present study showed that muscle mass increased significantly with exercise or essential AAS, although muscle strength, measured according to knee extension strength, improved significantly only in the exercise + AAS group.

Next, the discussion will focus on the changes in the combined variables. One study that investigated the effects of resistance exercise and nutritional supplementation on muscle mass and strength in older adults concluded that high-intensity resistance exercise was beneficial in increasing muscle mass and muscle strength, but the nutritional supplementation, which contained only a small percentage of a soy-based protein within a mixture of mainly carbohydrates, did not contribute to those gains.[8] As illustrated in Figure 2, exercise alone was effective in enhancing single variables such as leg muscle mass or usual walking speed. Similarly, the AAS group improved usual walking speed, but rationally, to treat sarcopenia, improvements in single variables are not sufficient. Improvements observed in the combined variables would presumably lead to the most-efficient reversal of sarcopenia. Significant improvements in the combinations of leg muscle mass, knee extension strength, and walking speed were seen only in the exercise + AAS group. Although whether exercise + AAS was better than either intervention alone remains inconclusive, these results suggest that exercise + AAS may be necessary for benefits in muscle mass and strength.

This study has several limitations. First is the measurement of body composition estimated using BIA. Although magnetic resonance imaging (MRI), computed tomography, and dual-energy X-ray absorptiometry are common, accurate clinical methods of measuring muscle mass,[30,31] they are cost ineffective and are not always appropriate for field studies. BIA is simple, noninvasive, and inexpensive and has been widely used in field studies. The comparison of MRI and BIA measurements has revealed a strong correlation between the two, confirming the validity of the BIA method for muscle mass measurement in older adults.[13,17,18] Therefore, the validity of the data collected using BIA has little influence on the interpretation of the results of this study. Second, it has been reported that AAS enhances muscle protein synthesis,[11,22,32] but the mechanism of the increase in muscle mass from AAS was not explored in the current investigation. Therefore, the results of this study were interpreted based on the assumption that muscle protein synthesis had been enhanced. Third, the effects of the exercise + AAS should have been determined with the use of placebos, but placebo treatments were not provided in this study, so future research should include placebos to observe the effects of exercise and AAS on physical function and muscle strength. Fourth, the total number of dropouts in this study was 11 people, and they were not included in the data analysis. Many studies have used intention-to-treat (ITT) analyses to determine the effects of RCTs, and the use of ITT analyses are increasing, although one previous study found that only approximately 35% of 274 RCTs used ITT analyses.[33] The current study was not an ITT analysis because it confirmed that there were no significant differences between the dropouts and the participants who completed the study, and the exclusion of the 11 dropouts from the analysis did not affect the integrity of the baseline randomization. Finally, previous research has shown that milk contains essential amino acids.[34,35] Because some of the participants took the AAS with milk, the exact essential amino acid dosage in this study could not be determined, and the effect of drinking milk on the results of this study was not confirmed. Future research should avoid the intake of milk with amino acids when investigating the effects of amino acids on muscle strength and mass and physical function.

This study demonstrated that exercise and nutrition may be necessary for the basic treatment of increasing muscle mass and strength to reverse the effects of sarcopenia in community-dwelling sarcopenic women. Exercise and AAS together have significant effects on enhancing not only muscle strength, but also the combined variables of muscle mass and walking speed and of muscle mass and strength in this study population, but further follow-up studies on larger populations are required to confirm these results.

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Author Contributions: H. Kim developed the study concept and design, recruited subjects, developed the intervention program, analyzed and interpreted the data, and prepared the manuscript. S. Takao interpreted the data and reviewed the manuscript for accuracy. K. Saito assisted in AAS and supervised the interview survey. Y. Hideyo assisted in subject recruitment, supervised the

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ORIGINAL PAPER

Plasma heat shock protein 72 as a biomarker of sarcopenia in elderly people

Kishiko Ogawa · Hun-kyung Kim · Takahiko Shimizu · Sigeaki Abe · Yumi Shiga · Stuart K. Calderwood

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Abstract Sarcopenia is a geriatric syndrome in which there is a decrease of muscle mass and strength with aging. In age-related loss of muscle strength, there are numerous observations supporting the assertion that neural factors mediate muscle strength. A possible contributing cause may be that aging changes systemic extracellular heat shock protein (eHsp)72 activity. The present study was designed to assess the plasma levels of eHsp72 in elderly people and to investigate its potential interaction with components of sarcopenia. A total of 665 men and women participated in an official medical health examination and an integrated health examination, including psychological and physical fitness tests. Blood samples were assayed for levels of plasma Hsp72, serum C-reactive protein, interleukin 6, tumor necrosis factor α, and regular biomedical parameters. We found that higher Hsp72 in plasma is associated with lower muscle mass, weaker grip strength, and slower walking speed, and may be a potential biomarker of sarcopenia in elderly people. This finding was supported by other results in the present study: (1) older age and shrinking body and lower hemoglobin levels, all of which characterize sarcopenia, were related to higher eHsp72 tertiles and (2) the ORs of the highest tertile of eHsp72 for the lowest tertiles of muscle mass, grip strength, and walking speed were 2.7, 2.6, and 1.8, respectively. These ORs were independent of age, sex, and the incidence of related diseases. Our results would reveal that eHsp72 in plasma is linked to sarcopenia factors and is a potential biomarker or predictor of sarcopenia.

Keywords Sarcopenia · Geriatric syndrome · Biomarkers · Extracellular Hsp · Skeletal muscle · Grip strength

Introduction

Sarcopenia is a geriatric syndrome in which there is a decrease of muscle mass and strength with aging

K. Ogawa (✉)
Research Team for Social Participation and Health Promotion,
Tokyo Metropolitan Institute of Gerontology,
35-2 Sakaecho,
Itabashi, Tokyo 173-0015, Japan
e-mail: kishiko@tmig.or.jp

H.-k. Kim
Research Team for Promoting Independence of the Elderly,
Tokyo Metropolitan Institute of Gerontology,
35-2 Sakaecho,
Itabashi, Tokyo 173-0015, Japan

T. Shimizu
Research Team for Molecular Gerontology,
Tokyo Metropolitan Institute of Gerontology,
35-2 Sakaecho,
Itabashi, Tokyo 173-0015, Japan

S. Abe
Department of Physical Education, Faculty of Sport Science,
Nippon Sport Science University,
7-1-1 Fukasawa, Setagaya,
Tokyo 158-8508, Japan

Y. Shiga
Department of Nursing, Faculty of Nursing,
Musashino University,
3-40-10 Sekimae Musashino-shi,
Tokyo 180-0014, Japan

S. K. Calderwood
Department of Radiation Oncology, Harvard Medical School,
Beth Israel Deaconess Medical Center,
Boston, MA 02215, USA

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(Rosenberg 1997). The prevalence of sarcopenia has been estimated at 5–13% of elderly people aged 60–70 years, and the numbers increase to 11–50% for those aged 80 or above (Haehling et al. 2010). It is a normal part of aging, but if unchecked, it can lead to weakness, disability, falls, loss of independence, and frailty (Roubenoff and Hughes 2000). Recently, the European Working Group on Sarcopenia in Older People developed a definition and diagnosis of sarcopenia (Cruz-Jentoft et al. 2010), introducing quantitative assessments of muscle mass, muscle strength, and physical performance, and established cutoff points based on measurements of muscle mass, grip strength, and gait speed. The International Working Group on Sarcopenia has also proposed criteria for diagnosing sarcopenia (Fielding et al. 2011), including gait speed and muscle mass. Unfortunately, since those cutoff points were based on data from specific ethnic groups, the utilization of these cutoff points or criteria could be limited. However, we may universally assess the data of muscle mass, grip strength, and gait speed with regard to the definition of sarcopenia, respectively. Sarcopenia has many causative factors, including a sedentary lifestyle and neurological, hormonal, nutritional, and immunological determinants (Roubenoff and Hughes 2000). Sarcopenic changes in the muscles include losses in muscle fiber quality and quantity, α-motor neurons, protein synthesis rates, and anabolic and sex hormone production (Waters et al. 2010). Many mechanisms have been proposed to cause the aforementioned sarcopenic changes, but the overall etiology is still not completely understood (Narici and Maffulli 2010). In age-related loss of muscle strength, there are numerous observations supporting the assertion that neural factors mediate muscle strength, and aging adaptations may involve changes in supraspinal drive generated from the cortex, coactivation of the antagonist muscle, as well as maximal spinal cord output and muscle coordination (Clark and Manini 2008). A possible contributing cause may be that aging changes systemic extracellular heat shock protein (Hsp) 72 activity.

Hsp are highly conserved proteins that are expressed both constitutively and under stressful conditions. The major role of Hsp appears to be the protection of the proteome via their molecular chaperone function. Hsp recognize damaged proteins and either channel such proteins into the repair/refolding pathways or to the proteolytic pathway (Lindquist and Craig 1988). In terms of cell survival, Hsp allow cells to respond to damage and begin the processes required to resolve cellular insults (Kampinga et al. 1995). Among the Hsp, the Hsp70 family is intrinsic to cellular life, permitting proteins to perform essential enzymatic reactions, signaling, and structural functions within the tightly packed milieu of the cell, and working to avert the catastrophe of protein aggregation during stress (Lindquist and Craig 1988; Georgopoulos and McFarland 1993). Hps70s are induced to extremely high levels by stress along with a cohort of other Hsp through powerful transcriptional activation, mRNA stabilization, and preferential translation (Lindquist and Craig 1988). Hsp72, which is a member of the Hsp70 family, circulates in the blood (Pockley et al. 1998), where it is referred to as an extracellular Hsp (eHsp, Fleshner et al. 2003).

Aging is associated with the degeneration of Hsp expression with time and the loss of resistance to cellular oxidants (Calderwood 2008). The effects of heat shock factor (Hsf)1 and Hsp on longevity appear to be particularly mediated through their ability to protect motor neurons (Calderwood 2008). It has been shown that the presence of eHsp72 can have a protective effect against necrotic cell death of smooth muscle cells (Johnson and Tytell 1993) and against apoptosis of motor neurons (Robinson et al. 2005). On the other hand, the elderly, even when considered healthy, frequently present systemic low-grade inflammation (Ogawa et al. 2010). It has shown that interleukin (IL)-1β, IL-6, and TNF-α levels in elderly people are related to severe muscle wasting and cachexia (Roubenoff and Hughes 2000), because these inflammatory cytokines are involved in the muscle catabolic processes associated with inflammation (Degens 2010).

While eHsp72 can have a protective effect against apoptosis of motor neurons (Robinson et al. 2005) for the muscle anabolic process, based on the category of sarcopenia, it has been hypothesized that inflammatory cytokines and eHsp72 have independent effects that are potentially associated with prevalent sarcopenia. Thus, whereas inflammatory cytokines are related to muscle catabolism, eHsp72 might be related to anabolic protection of motor neurons. Investigating this hypothesis will help advance our understanding of the involvement of these two distinct components of sarcopenia mechanisms. To test this hypothesis, a cross-sectional analysis of data from the Kusatsu study was conducted, evaluating the associations between prevalent lower muscle mass, grip strength, and gait speed, individually and in combination.

Methods

Subjects

A total of 665 participants aged 65–96 years living in a community setting participated in an official medical health examination for community residents administered by the local government of Kusatsu, Gunma. The total population aged 65 or over was 1,928. All of the

elderly people received information on an official medical health examination for community residents by post. Therefore, the ratio of those having the medical examination was 34% (665/1,928). The sex ratio distribution of the participants was significantly different from a random distribution (male, n=264; female, n=356; P<0.001), but there were no significant differences in the mean ages between the sexes [mean± standard deviation (SD): male 73.5±6.0 years, female 73.4±6.3 years]. All participants were informed of the purpose and risks of the study before giving written informed consent. This study was conducted in accordance with the Declaration of Helsinki, and its protocol was approved by the ethics committee at Tokyo Metropolitan Institute of Gerontology.

Assessment of functional health status, lifestyle, and life satisfaction, and measurement of physical performance

Functional health status, lifestyle, and life satisfaction can possibly confound sarcopenia symptoms. To examine healthiness, the lack of which leads to low daily activity and low total energy expenditure, functional health status was assessed using six parameters: (1) poor hearing, (2) poor sight, (3) walking aid, (4) bathing, (5) dressing, and (6) toileting status. To examine daily activity and locomotive status, which is related to low activity and other factors that reflect on chronic diseases, lifestyle was assessed by five parameters: (1) shopping, (2) cooking, (3) frequency of outdoor activity, (4) alcohol drinking status, and (5) smoking status. To examine mental health status, which is related to low daily activity, life satisfaction was assessed by self-rated health (1–4, score 4 represents self-reported unhealthy status), Geriatric Depression Scale (0–15, a total score of 15 represents depressive moods), and Mini-Mental State Examination (0–30, a total score of 30 represents normal cognitive condition).

The physical performance test consisted of grip strength and walking speed (Suzuki et al. 2003; Studenski et al. 2011; Cooper et al. 2010). The grip strength of the preferred hand was measured two times using a handheld Smedly-type dynamometer. The higher value was adopted. In the walking test, the participant walked along a straight walkway of 11 m on a flat floor. The speed and number of steps were measured for the middle 5-m portion of the walkway. The participant took the test by walking at a preferred speed two times, and the faster speed was recorded.

Clinical history and medical examination

In the medical examinations, body height (using a body height meter), body weight, and skeletal muscle mass were measured using bioelectrical impedance analysis systems (InBody; BIOSPACE, Tokyo, Japan). During the medical examination, a blood sample was collected from the antecubital vein for routine hematological and biochemical tests, including white blood cell count, hemoglobin, albumin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Clinical histories and medical examinations were carried out by physicians.

Blood sampling for other laboratory assays

Blood samples were collected from the antecubital vein for plasma in a tube containing 30 μl of EDTA, and serum in a plain tube, and spun at 1,000×g at 4°C for 10 min, and the supernatant was stored at −80°C until analysis. For analysis of eHsp72, enzyme-linked immunosorbent assay (ELISA) kits were used to measure the plasma concentrations of Hsp72 (#ADI EKS-715; Enzo Life Sciences, Inc. NY, USA). Serum C-reactive protein (CRP), IL-6, β2-microglobulin (β2-MG), and tumor necrosis factor (TNF)-α levels were measured using ELISA and enzyme immunoassay, respectively (SRL Co., Tokyo, Japan). The interassay coefficient of variance was 3.6–11.1%. The intra-assay coefficient of variance was 4.6–9.2%.

Statistics

Average values and SD are given in the total numbers of age results. However, eHsp72 had a non-normal distribution as evaluated using the Kolmogorov–Smirnov test (P<0.01). As a consequence, in the analysis of these parameters, nonparametric tests were used when comparing and correlating the parameters according to eHsp72 levels. Median and interquartile range (25–75th percentile) or average values±SD are given in the "Results" section, depending on the measured level.

Age differences in eHsp72 were analyzed using Kruskal–Wallis analysis as shown in Fig. 1. Sex differences in eHsp72 in the same age groups were analyzed using the Mann–Whitney test as shown in Fig. 1. The subjects were classified according to tertile levels of eHsp72 shown in Table 1. We then analyzed anthropometric variables, physical fitness variables, biochemical variables, and inflammatory biomarkers using the Jonckheere–Terpstra test to compare the tertile groups. Since sex differences might have biased the relationships between physical fitness variables and other parameters, the values based on eHsp72 tertiles were expressed as totals for men and women separately. The associations between eHsp72 levels and these variables are represented by Spearman correlation coefficients shown in Table 2 and Fig. 2A–C.

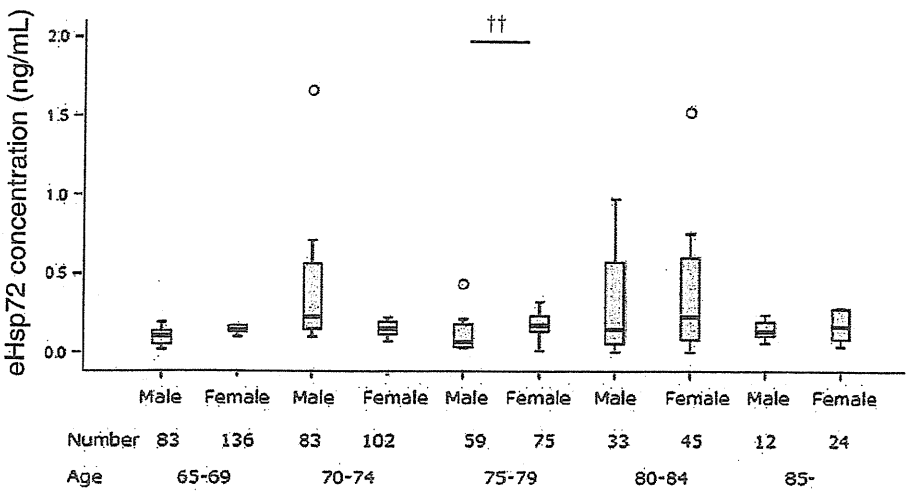

Fig. 1 Box and whisker plots on plasma levels of eHsp72 by age group and sex. Significant differences between sexes in the same age group were analyzed using Mann–Whitney analysis. ††$P<0.01$. *Circles* outliter. No differences were found between any of the age groups within the same sex, as analyzed using Kruskal–Wallis analysis

Previous studies have shown that diseases are known confounding factors of sarcopenia (Fried et al. 2001) and can trigger it; diseases induce lower physical activity or disuse of muscle. To test which diseases might influence eHsp72 levels, differences in eHsp72 tertiles between patients were evaluated using the Jonckheere–Terpstra test. To examine whether serious underlying diseases confounded the association of eHsp72 with sarcopenia, odds ratios were derived from multiple logistic regression analysis of eHsp72 tertiles adjusted by sex, age, and the incidence of disease (Table 3).

To better understand the gradient of weaker muscle strength risk associated with combined levels of IL-6 and eHsp72, differences in grip strength were explored according to the five combination groups using multiple logistic regression analysis (Leng et al. 2007; Bautmans et al. 2007). For grip strength, values were divided into two groups: a lower strength group (below one SD of the average value) and a higher strength group (above one SD of the average value) with men and women, respectively. To explore potential synergy between IL-6 and eHsp72 tertile levels, we divided five mutually exclusive groups in increasing order of severity: group 1—IL-6 bottom tertile + eHsp72 bottom tertile (the reference group); group 2—IL-6 bottom + eHsp72 middle, and IL-6 middle+eHsp72 bottom; group 3—IL-6 bottom + eHsp72 top, IL-6 top + eHsp72 bottom, and IL-6 middle + eHsp72 middle; group 4—IL-6 middle + eHsp72 top, and IL-6 top + eHsp72 middle; and group 5—IL-6 top+eHsp72 top (Leng et al. 2007). The analyses were adjusted for age and sex (Fig. 3).

All reported P values were two tailed, and the level of significance was set at $P<0.05$. Statistical analysis was performed using IBM SPSS version 19 for Japanese (Nihon IBM Inc., Tokyo, Japan).

Results

eHsp72 profiles in relation to age and sex

The number of total subjects was 665; however, the plasma levels of eHsp72 in 13 subjects were undetectable. The plasma levels of eHsp72 with sex and age groups are shown in Fig. 1. A significant interaction in the age groups was not found using Kruskal–Wallis analysis. In the age group 75–79, eHsp72 in female subjects was higher than that in male subjects. However, there were no significant differences between the sexes in the other age groups. No differences were found between any of the age groups.

Anthropometrics, physical fitness, and biomarker profiles in relation to eHsp72 tertiles

When eHsp72 levels were divided into three equally spaced categories (tertiles), the cutoff values for eHsp72 tertiles were as follows: the lowest tertile of eHsp72 was under 0.12 ng/mL, the middle tertile was 0.13–0.22, and the highest tertile was over 0.23 ng/mL ($P<0.01$). The anthropometric, physical fitness, and biomarker profiles in relation to the eHsp72 tertiles are summarized in Table 1. Using the Jonckheere–Terpstra test, we found significant higher in age (both sexes and females) stepwise from low eHsp72 to middle eHsp72 to high eHsp72 tertiles. They were significantly lower in height (both sexes), weight (both sexes), muscle volume (both sex and males), grip strength (both sexes and males), and walking speed (both sexes and females) increasing stepwise from low eHsp72 to middle eHsp72 to high eHsp72 tertiles (Table 1).

Among the biomarkers and the inflammatory markers, there was a significant decrease in hemoglobin (Hb) levels

Table 1 Median and interquartile ranges of anthropometric physical fitness factors flammatory and biomarker levels in relation to tertiles of eHsp72

	Lowest (<0.13 ng/mL)		Middle (0.13–0.22 ng/mL)		Highest (0.22<ng/mL)		Jonckheere–Terpstra	
Male/female (*n*)	109/120		85/122		76/140		Total	270/382
	Median	IQR	Median	IQR	Median	IQR	*P* value	
Hsp72 (ng/mL)								
Total	0.08	0.05–0.11	0.16	0.14–0.19	0.53	0.29–0.95	0.000*	
Male	0.09	0.04–0.11	0.16	0.14–0.19	0.54	0.31–0.91	0.000*	
Female	0.07	0.05–0.11	0.16	0.14–0.18	0.52	0.28–1.06	0.000*	
Age (year)								
Total	72	68–77	71	68–76	73	69–78	0.040**	
Male	72	68–77	72	68–77	73	69–79	0.427	
Female	71	67–78	71	68–76	74	69–78	0.035**	
Height (cm)								
Total	154	148–162	153	147–160	151	146–158	0.002*	
Male	162	158–165	161	157–165	159	157–164	0.067	
Female	148	143–153	149	144–153	147	144–151	0.441	
Weight (kg)								
Total	56	49–64	53	47–61	53	46.2–59.5	0.005*	
Male	61	55–68	60	53–65	58	52–66	0.079	
Female	51	44–58	50	45–55	50	44–57	0.611	
Muscle volume (kg)								
Total	21.1	17.6–24.7	19.9	17.4–23.6	18.8	17–22.4	0.000*	
Male	24.7	22.8–27.1	24.3	22.2–26.4	24	21.5–26	0 0.023**	
Female	17.8	15.6–19.9	18	16.2–19.5	17.8	15.9–18.9	0.222	
Grip strength (kg)								
Total	24.8	19.6–34.0	24.0	19.5–31.3	22.5	18.4–29.0	0.005*	
Male	34.5	30.0–38.5	33.0	28.5–37.0	32.5	26.5–37.0	0.029**	
Female	20.0	16.8–22.5	21.0	16.8–24.0	19.5	16.5–22.5	0.722	
Walking speed (m/s)								
Total	1.38	1.22–1.56	1.37	1.22–1.52	1.30	1.1–1.5	0.002*	
Male	1.43	1.25–1.56	1.39	1.25–1.52	1.37	1.2–1.6	0.068	
Female	1.39	1.19–1.52	1.35	1.19–1.52	1.28	1.1–1.4	0.037**	
CRP (U/L)								
Total	602	274–1,027	510	222–1,070	562	271–1,140	0.874	
Male	624	247–1,150	510	239–1,300	602	302–1,200	0.730	
Female	590	277–1,010	510	217–870	491	231–1,090	0.728	
IL–6 (pg/mL)								
Total	2.0	1.3–2.5	1.9	1.2–2.9	1.91	3–3.0	0.399	
Male	2.1	1.5–2.7	2.1	1.3–3.4	2.0	1.4–2.8	0.890	
Female	1.7	1.2–2.5	1.9	1.2–2.6	1.9	1.3–3.1	0.210	
TNF-α (pg/mL)								
Total	1.2	0.9–1.6	1.1	0.9–1.5	1.3	0.9–1.9	0.079	
Male	1.2	0.9–1.7	1.2	1.0–1.6	1.5	1.1–2.2	0.010**	
Female	1.2	0.9–1.5	1.1	0.8–1.4	1.2	0.9–1.7	0.570	
β2-MG (mg/L)								
Total	1.8	1.6–2.1	1.8	1.5–2.0	1.8	1.6–2.3	0.065	
Male	1.9	1.6–2.1	1.9	1.6–2.2	1.9	1.6–2.3	0.620	
Female	1.8	1.5–2.1	1.7	1.5–2.0	1.8	1.6–2.3	0.016**	

Table 1 (continued)

Male/female (*n*)	Lowest (<0.13ng/mL) 109/120		Middle (0.13–0.22ng/mL) 85/122		Highest (0.22<ng/mL) 76/140		Jonckheere–Terpstra Total 270/382
	Median	IQR	Median	IQR	Median	IQR	*P* value
WBC/mL							
Total	5,400	4,500–6,400	5,500	4,400–6,500	5,300	4,525–6,175	0.579
Male	5,500	4,600–6,500	5,600	4,300–6,600	5,400	4,525–6,200	0.900
Female	5,300	4,425–6,175	5,450	4,400–6,425	5,200	4,525–6,075	0.620
Hb (g/dL)							
Total	13.9	13–14.9	13.6	12.9–14.5	13.6	12.7–14.3	0.005*
Male	14.9	14.1–15.5	14.5	13.4–15.4	14.4	13.8–15.3	0.040**
Female	13.1	12.6–13.9	13.3	12.7–13.9	13.2	12.6–13.8	0.530
Albumin (g/dL)							
Total	4.2	4.0–4.4	4.2	4.0–4.4	4.2	4.0–4.3	0.234
Male	4.2	4.0–4.4	4.2	4.0–4.3	4.2	4.0–4.4	0.375
Female	4.2	4.0–4.3	4.2	4.1–4.4	4.2	4.0–4.3	0.335
LDL-Cho (mg/dL)							
Total	114	95–135	114	95–138	116	98–138	0.439
Male	109	90–132	107	86–128	114	97–137	0.290
Female	117	102–141	123	101–141	118	98–138	0.660
Triglyceride (mg/dL)							
Total	132	86–189	126	90–185	122	88–159	0.187
Male	139	80–197	127	84–185	126	87–189	0.600
Female	122	88–185	123	93–185	119	89–153	0.198
HDL-Cho (mg/dL)							
Total	55	47–66	56	48–65	58	48–67	0.296
Male	53	45–61	52	45–61	53	44–62	0.910
Female	60	49–69	60	50–67	60	50–69	0.676

IQR interquartile range, *β2-MG* β2-microgrobulin, *WBC* white blood cells, *Hb* hemoglobin, *LDL-Cho* low-density lipoprotein, *HDL-Cho* high-density lipoprotein

*$P<0.01$; **$P<0.05$, using Jonckheere–Terpstra

(both sexes and males) stepwise from low eHsp72 to middle eHsp72 to high eHsp72 tertiles. They were significantly higher in TNF-α levels in males increasing stepwise from low eHsp72 to middle eHsp72 to high eHsp72 tertiles. β2-MG levels in females, both in the lowest and highest tertiles of eHsp72, were higher than that in the middle tertile group (Table 1).

Correlation analysis in relation to eHsp72 concentration

Correlation coefficients are shown in Table 2 and Fig. 2a–c. Height, weight, skeletal muscle volume, grip strength, walking speed, and Hb in total subjects were associated with lower eHsp72 (negative correlation). TNF-α in male subjects was positively correlated with eHsp72 (Table 2).

Multiple logistic regression analysis

For disease history, no significant trends for eHsp72 tertiles among the specific diseases were found. Previous studies have shown that diseases are known confounding factors of sarcopenia (Fried et al. 2001) and can trigger it. Sarcopenia, including the accompanying lower physical activity, can, in turn, induce diseases. To confirm that no diseases seriously confounded the association of eHsp72 with sarcopenia, we performed logistic regression analysis of eHsp72 tertiles with additional adjustments for age, sex and the incidence of disease (e.g., the incidence of other disease). Table 3 shows the odds ratios for muscle mass, grip strength, and walking speed, adjusted sex, age, and the incidence of disease. The highest tertile of eHsp72 retained significant associations with the lowest tertile of skeletal muscle

Table 2 Significant Spearman correlations between eHsp72 and other variables

	Hsp72	
	r	*P* value
Height		
Total	−0.106	0.008*
Male	−0.085	0.168
Female	−0.023	0.664
Weight		
Total	−0.095	0.017**
Male	−0.060	0.336
Female	−0.020	0.703
Muscle volume		
Total	−0.138	0.001*
Male	−0.104	0.092
Female	−0.055	0.295
Grip strength		
Total	−0.111	0.006*
Male	−0.111	0.075
Female	−0.037	0.485
Walking speed		
Total	−0.117	0.004*
Male	−0.093	0.140
Female	−0.114	0.034**
TNF-α (pg/mL)		
Total	0.062	0.139
Male	0.164	0.012**
Female	0.013	0.804
Hb		
Total	−0.090	0.022**
Male	−0.088	0.149
Female	−0.026	0.619

Total n=652, male n=270, female n=382

TNF tumor necrosis factor, *Hb* hemoglobin

*P<0.01; **P<0.05

mass [odds ratio (OR), 2.72; 95% confidence interval (CI), 1.21–6.16, P<0.01], the lowest tertile of grip strength [OR 2.60, 95% CI 1.17–5.81; P<0.01], and the lowest tertile of walking speed [OR 1.82, 95% CI 1.03–3.20; P<0.01] using logistic regression models (Table 3).

Combined IL-6 and eHsp72 levels and weaker hand grip

Figure 3 shows the odds ratio of risks for weaker hand grip with combined levels of IL-6 and eHsp72 level. We divided five mutually exclusive groups in increasing order of severity: group 1—76 participants IL-6 bottom tertile + eHsp72 bottom tertile (the reference group); group 2—168 participants IL-6 bottom + eHsp72 middle, and IL-6 middle + eHsp72 bottom; group 3—197 participants IL-6 bottom + eHsp72 top, IL-6 top + eHsp72 bottom, and IL-6 middle + eHsp72 middle; group 4—120 participants IL-6 middle + eHsp72 top, and IL-6 top + eHsp72 middle; and group 5—69 participants IL-6 top + eHsp72 top. For weaker hand grip strength, only those in the group 4 (IL-6 middle + eHsp72 top, and IL-6 top + eHsp72 middle) had significantly higher risk for being weaker hand grip strength [OR 3.31, 95% CI 1.48–7.41], adjusted age, and sex.

Discussion

We focused on the biological significance of eHsp72 in elderly people. We demonstrated that higher Hsp72 in plasma is associated with lower muscle mass, weaker grip strength, and slower walking speed, and is a potential biomarker of sarcopenia in elderly people. This finding was supported by other results in the present study: (1) older age and shrinking body (i.e., shorter height and lighter body weight) and lower hemoglobin levels, all of which characterize sarcopenia, were related to higher eHsp72 tertiles and (2) the ORs of the highest tertile of eHsp72 for the lowest tertiles of muscle mass, grip strength, and walking speed were 2.7, 2.6, and 1.8, respectively. These ORs were independent of age, sex, and the incidence of related diseases (Table 3).

We also found that inflammatory cytokines and eHsp72 were independent and potentially associated with prevalent sarcopenia. Group 4 (IL-6 middle + eHsp72 top, and IL-6 top + eHsp72 middle) had a significantly higher risk for being in the weaker grip strength group (R 3.31, 95% CI 1.48–7.41; P=0.004) compared to group 5 (IL-6 top + eHsp72 top). One possible explanation is that IL-6 and eHsp72 negate each other. These results might imply that eHsp72 reflects the opposite status of inflammation. Bautmans et al. (2008) investigated the effect of IL-6 and eHsp72 on muscle endurance in elderly nursing home residents, and demonstrated that subjects with both high serum levels of IL-6 and eHsp72 had worse muscle endurance compared to those with high IL-6 and low eHsp72, or with low IL-6 and high eHsp72. They pointed out the possibility that the response of eHsp72 to exercise might reflect the anti-inflammatory status of elderly people, which might support our present results. Clark and Manini (2008) suggested the term "dynapenia" to specifically describe the age-associated loss of muscle strength. They argued that (1) longitudinal aging studies indicate a disassociation between the loss of muscle mass and strength and (2) the changes in muscle mass and the changes in

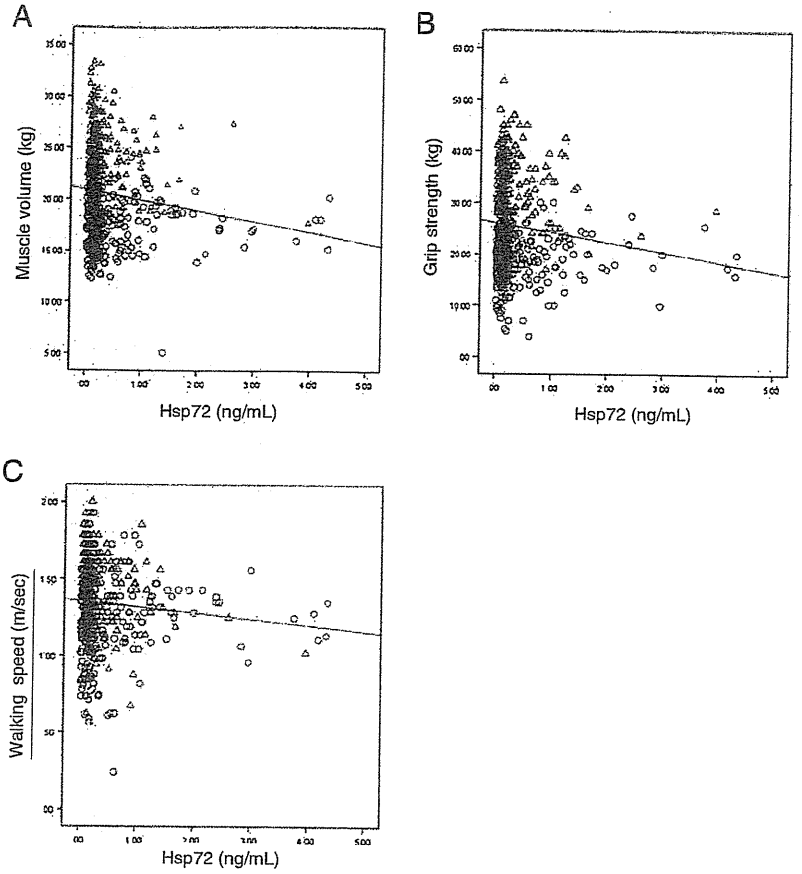

Fig. 2 **a** Regression plot of Hsp72 levels in plasma and muscle volume. *Circles* female, *triangles* male. $R=-0.138$, $P=0.001$, as analyzed using Spearman correlation. **b** Regression plot of Hsp72 levels in plasma and grip strength. *Circles* female, *triangles* male. $R=-0.111$, $P=0.006$, as analyzed using Spearman correlation. **c** Regression plot of Hsp72 levels in plasma and walking speed. *Circles* female, *triangles* male. $R=-0.117$, $P=0.004$, as analyzed using Spearman correlation

strength resulting from alterations in physical activity levels (i.e., exercise training or disuse) do not follow the same time course, suggesting that the human neuromuscular system must be involved in the regulation of strength (Clark and Manini 2008). Since eHsp72 (Asea et al. 2000) is involved in the inflammatory cytokine cascade yielding

Table 3 Sarcopenia factors associated with eHsp72 levels in plasma, adjusted for age and sex

Male/female (*n*)	Lowest (<0.13 ng/mL) 109/120 Reference	Middle (0.13–0.22 ng/mL) 85/122 OR [95% CI]	Highest (0.22<ng/mL) 76/140 OR [95% CI]
Muscle mass tertile			
Low	1	2.379 [1.067–5.303]	2.724 [1.205–6.157]
Middle	1	2.143 [1.119–4.105]	2.226 [1.143–4.335]
High	1 (reference)	1	1
P for trend		0.041	0.016
Grip strength tertile			
Low	1	1.076 [0.482–2.402]	2.604 [1.168–5.805]
Middle	1	1.375 [0.715–2.645]	2.270 [1.181–4.362]
High	1 (reference)	1	1
P for trend		0.858	0.019
Walking speed tertile			
Low	1	1.322 [0.766–2.283]	1.815 [1.029–3.202]
Middle	1	1.459 [0.892–2.388]	1.802 [1.068–3.042]
High	1 (reference)	1	1
P for trend		0.316	0.040

Adjusted age, sex, and the incidence of other diseases

OR odds ratio, *95% CI* 95% confidence interval

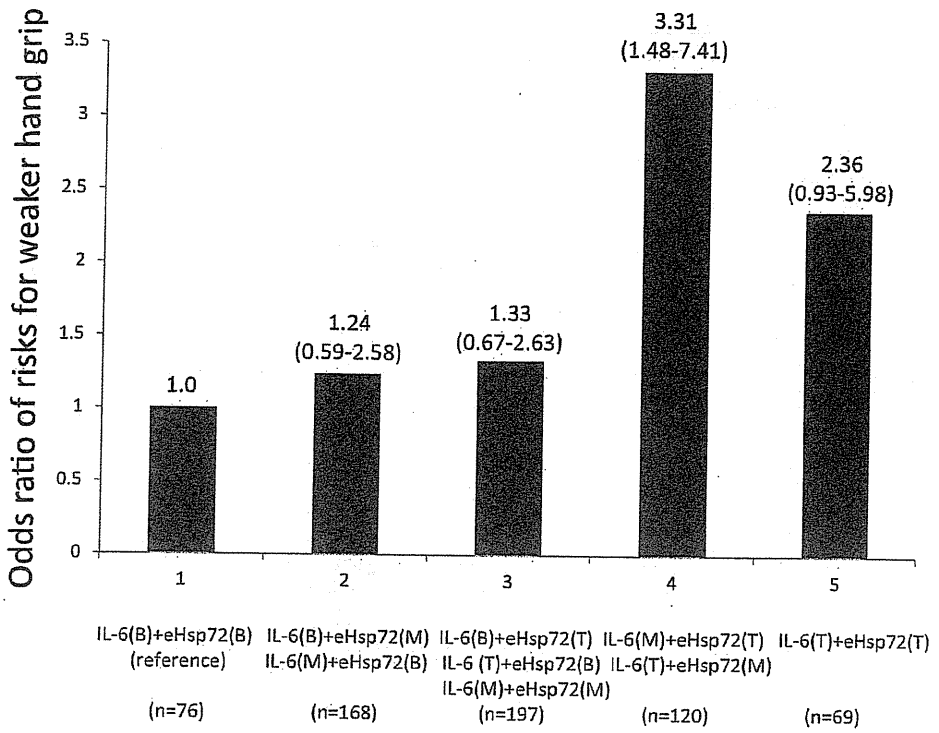

Fig. 3 Odds ratio of risks for weaker hand grip. Subjects were grouped based on their tertiles of IL-6 levels and eHsp72 levels. *B* bottom tertile, *M* middle tertile, *T* top tertile (95% CI)

IL-6 and is known to function as a cytokine, this has prompted us to consider it as an inflammatory factor; however, it also plays a role as an anti-inflammatory factor. Accordingly, it might be that inflammatory cytokines are related to muscle mass changes per se (i.e., sarcopenia), including muscle catabolism and synthesis, whereas eHsp72 is related to muscle strength for the protection of motor neurons (i.e., dynapenia).

Interestingly, in the nervous system, as in other tissues, the induction of Hsps not only serves as a marker for stress but has a protective effect as well (Tidwell et al. 2004). It is generally assumed that a cell must produce its own proteins (e.g., Hsps) to be protected by them (Lasek et al. 1977). Robinson et al. demonstrated that not only expressed Hsp72 but also extracellular Hsp72 plays a role after stress to promote the maintenance of survival pathways and/or inhibit the activation of cell death-specific events in motoneurons (Robinson et al. 2005). They claimed that considering the size of and metabolic demands on motoneurons, it is possible that these cells are only capable of synthesizing amounts of Hsc70 or Hsp70 necessary for the maintenance of cell function and survival. The cells do not appear able to increase production in response to the greater demands of stressful stimuli. The extracellular Hsp72 derived from other cell types may compensate for this deficit (Robinson et al. 2005).

Acute bouts of aerobic exercise induce eHsp72 elevation (Walsh et al. 2001). This elevation is transient; once the stressor (i.e., exercise) is removed, the levels of eHsp72 return to normal. At the resting level in young humans, Hsp72 concentrations in cerebrospinal fluid (CSF) are threefold higher than in plasma (Steensberg et al. 2006), suggesting enhanced neuronal stress tolerance (Guzhova et al. 2001). However, whether acute exercise contributes to the system or not remains unknown, because the CSF levels of Hsp72 are not affected by 2 h of exhausting exercise (Steensberg et al. 2006). However, a study has shown that a 12-week resistance training program induces a reduction of eHsp72 in elderly women (Ogawa et al. 2010), and centenarians are an exception in that they have decreased eHsp72, suggesting that lower eHsp72 leads to healthy outcomes later in life (Terry et al. 2004). Accordingly, higher eHsp72 may relate to unhealthier conditions in aged people, as our results implied. On the other hand, a number of studies have reported reduced levels of circulating Hsp70 in the elderly, and some more historic data have indicated that the ability to mount a stress response is decreased with aging (Rea et al. 2001). Results from cultured cells suggest that the age-related decline in Hsp70 expression is constitutive and is due to decreased binding of the heat shock factor (Hsf) 1 to the heat shock element (Hse) and diminished Hsp 70 transcription (Horowitz and Robinson 2007). Alternatively, there may be an age-associated increase in abnormal or denatured proteins that could interfere with Hsf biding to Hse (Munro and Pelham 1985). Since mitochondria in old animals are more

vulnerable to incurring and less able to repair oxidative damage that occurs in response to a physiologically relevant heat stress, an increase in free radical production and oxidative damage with aging might induce a decrease in stress tolerance at both cellular and whole-organism levels (Haak et al. 2009). In vivo, severe ATP depletion can cause destabilization and aggregation of many proteins (Kabakov et al. 2002). If Hsp70, a known ATP-dependent chaperone induced by the appearance of denatured proteins within a cell following stress, is not being properly induced in old rats following heat stress (Fargnoli et al. 1990), the resultant subcellular stress caused by the toxic accumulation of protein aggregates could be significant enough to cause damage to mitochondria, peroxisomes, rough endoplasmic reticulum, and membrane lipids (Oberley et al. 2008). Interestingly, decreased ATP levels in old rats compared with young throughout most of recovery time course indicated an overall decreased ability of senescent animals to compensate for a loss in energy metabolism (Oberley et al. 2008). Mechanisms for an attenuated stress response in aging remain complex and unknown, and this warrants further investigation.

The present investigated the biological significance of eHsp72 in an elderly population. Our results would reveal that eHsp72 in plasma is linked to sarcopenia factors and is a potential biomarker or predictor of sarcopenia. Geriatric syndromes have a biological basis and are considered to be highly prevalent and carry a high risk for adverse health outcomes. The present results could lead to the development of methods for screening those who require effective, targeted care.

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地域在住高齢者におけるサルコペニア改善のための運動，アミノ酸補充の効果

[1]東京都健康長寿医療センター研究所，[2]味の素株式会社，
[3]国立長寿医療センター研究所
金　憲経[1]，齋藤京子[1]，吉田英世[1]，加藤弘之[2]，小林久峰[2]，片山美和[2]，鈴木隆雄[3]

Effects of exercise and amino acid supplementation for sarcopenia in community-dwelling elderly people

Hun-kyung Kim[1], Kyoko Saito[1], Hideyo Yoshida[1], Hiroyuki Kobayashi[2], Hisamine Kato[2], Miwa Katayama[2] and Takao Suzuki[3]

[1]Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
[2]Ajinomoto Co. Inc., Kawasaki, Japan
[3]National Institute for Longevity Sciences, Aichi, Japan

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[1]東京都健康長寿医療センター研究所，[2]味の素株式会社，
[3]国立長寿医療センター研究所
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Hun-kyung Kim[1], Kyoko Saito[1], Hideyo Yoshida[1], Hiroyuki Kobayashi[2], Hisamine Kato[2], Miwa Katayama[2] and Takao Suzuki[3]

[1]Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
[2]Ajinomoto Co. Inc., Kawasaki, Japan
[3]National Institute for Longevity Sciences, Aichi, Japan

はじめに

人間の諸機能は，常に変化する属性を持ち，個体の潜在能力が効率よく発揮できる方向へ変えていくのが一般的である。しかし，中年期を過ぎると様々な組織の機能が十分発揮できなくなり，環境変化への適応能力の低下ないしは機能喪失が徐々に増してくる。その背景要因の一つに，体脂肪やLBM（lean body mass）の変化が挙げられる[1]。中でも，骨格筋量の減少（Sarcopenia）[2]は，筋力の衰え，身体機能の低下をもたらし，身体的障害あるいは老年症候群の発症と密接に関わっていることが多くの疫学調査で指摘されている。骨格筋量の減少には性，年齢，身長，体重，BMI，テストステロン，脂肪量，不活動，ビタミンD，低栄養など様々な要因が複雑に関わっている[3,4]。サルコペニア予防策を構築するためには，多くの危険因子の中で，可変因子の改善を目的とした取組みが有効であり，Fiataroneら（1994）は，骨格筋の不使用と低栄養の改善に焦点を当てた介入が有効であると指摘している[5]。

サルコペニア予防のための戦略

加齢に伴う骨格筋量の減少を予防したり，委縮した骨格筋の機能を回復させるためには，筋に適当な刺激を与えるトレーニングが有効的と考える。しかし，虚弱高齢者を対象とする場合には，筋力発揮に伴うメカニカルストレスの増大や循環器への負担が懸念され，無理のないトレーニングが原則である。運動効果について調べた研究によれば，日常的活動レベルが低く，筋力低下が進んでしまった虚弱高齢者であっても筋力増大の効果が報告されている。虚弱高齢者における著しい筋力増大効果は，筋肥大よりも神経系の機能改善に起因するものと考えられてきた。しかし，最近の研究により高齢者でも筋肥大が起こることが確かめられている[5]。

Fiataroneら（1994）は，72～98歳の長期施設入所者100名を対象に，筋力強化運動，栄養補充効果を検証した。その結果，筋力強化運動群では筋力113%（P<0.01），歩行速度11.8%（P=0.02），階段昇降機能28.4%（P=0.01）と有意に上昇したが，太腿の筋断面積2.7%（P=0.11）増加に止まった。一方，240mlの栄養補充（炭水化物60%，脂肪23%，タンパク質17%）の効果は検証されなかったと指摘している[6]。これらの結果は，サルコペニアの改善のためには単なる栄養補充ではなくて，骨格筋量の減少メカニズムを把握した上での処置が必要であることを示唆する試験である。高齢者における骨格筋量の減少（サルコペニア）背景は，高齢者では，筋タンパク質の合成と分解が減弱し，その結果としてサルコペニアが起こるということである。よって，骨格筋量の予防・改善には筋タンパク質合成促進が有効と考える。骨格筋タンパク質合成は血液中のアミノ酸濃度に影響され，血液中のアミノ酸濃度が上昇すると筋タンパク質合成速度が速やかに増加するが，分解速度は変化しないことが指摘されている[7]。特に，高ロイシン含量の必須アミノ酸は比較的少量で筋タンパク質合成が促進されることを検証したことから，その長期摂取による骨格筋量の改善が期待できる[8]。

サルコペニア改善のための運動，アミノ酸補充の効果

1）サルコペニア高齢者の特徴

これらの背景を踏まえて，筆者は，サルコペニアと判定された304名と正常者1,095名の調査項目を比較し，サルコペニア高齢者の特徴を調べた。その結果，サルコペニア群は正常群に比べて，年齢が高く，下腿三頭筋周囲，BMI，筋肉量が有意に低値を示すとともに，健康度自己

表１．サルコペニア群と正常群の調査項目の比較

項　目	サルコペニア群	正常群	p値
年齢（歳）	79.49 ± 2.93	78.51 ± 2.77	<0.001
下腿三頭筋周囲（cm）	30.17 ± 2.03	33.92 ± 2.60	<0.001
ＢＭＩ（kg/m^2）	18.98 ± 2.01	23.74 ± 2.84	<0.001
筋肉量（kg）	26.92 ± 2.61	31.73 ± 3.16	<0.001
健康度自己評価，健康（%）	75.7	85.8	<0.001
外出頻度，少ない（%）	4.6	2.5	0.051
運動習慣，有（%）	27.3	33.5	0.039
既往歴，有（%）			
高血圧	51.0	58.0	0.029
高脂血症	32.2	40.5	0.009
貧血症	4.6	2.2	0.022
骨粗鬆症	38.2	30.7	0.014
骨折	28.6	22.9	0.038

評価，定期的な運動習慣を持っている者の割合は低かったが，外出頻度低下者の割合は高かった。一方，既往歴においては，貧血症，骨粗鬆症，骨折歴は有意に高かったが，高血圧症，高脂血症は正常群より低かった（表１）。

２）運動，アミノ酸補充の効果

サルコペニア改善のための運動，アミノ酸補充の効果を検証するために，介入参加希望者をRCTにより運動群と栄養群に分け，運動群には週２回，１回当たり60分間の筋力強化と歩行機能の改善を目的とした包括的運動指導を，栄養群にはロイシン高配合のアミノ酸３gを１日２回補充する指導を，３ヶ月間実施した。介入前後における身体組成，体力，老年症候群の改善の度合いを検討した。その結果，LBMは運動群で2.4%，栄養群で4.6%の有意な向上が，歩行速度は，運動群で18.6%，栄養群で10.3%の顕著な向上が確認され（図１），地域在住サルコペニアの改善には運動のみならずアミノ酸補充も有効であることが示唆された。しかし，サルコペニア高齢者に多く観察される尿失禁は，運動群で38.9%から

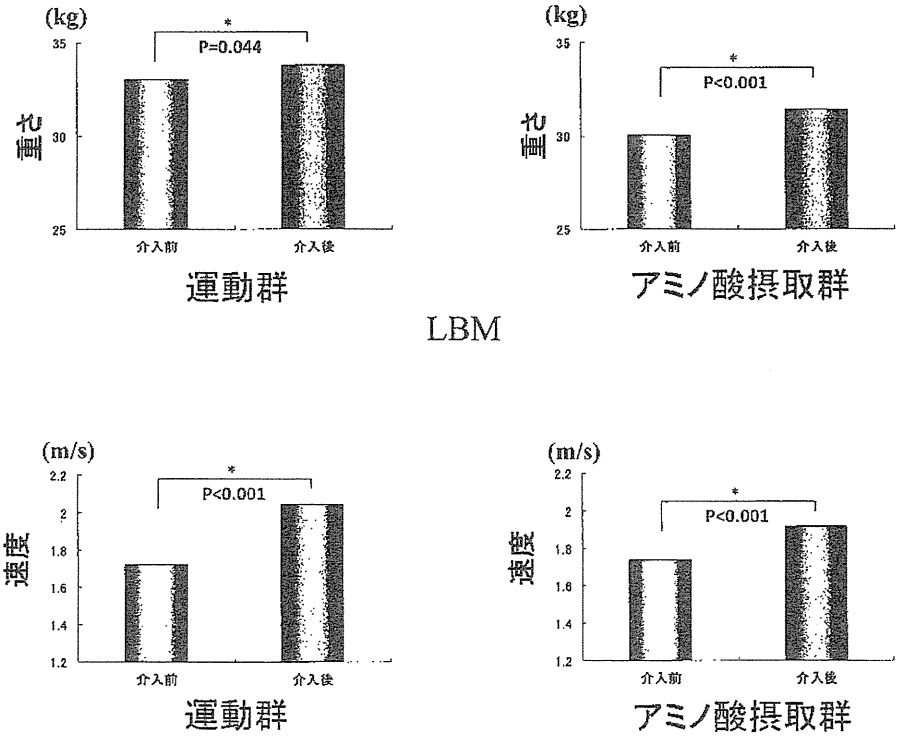

図１．３ヶ月間の運動，アミノ酸摂取の介入がLBMおよび歩行速度に及ぼす影響

19.4% (P=0.021) と有意に改善されたが，栄養群では有意な改善が見られなかった。以上のことから，サルコペニア高齢者のLBMあるいは体力の改善を目的とした場合には，運動指導あるいは栄養補充の両方とも有効な手法であることが確認されたが，サルコペニア高齢者に有症率の高い老年症候群の改善のためには，運動介入の効果が優れる可能性が示唆された。

おわりに

骨格筋量の減少に伴う筋力の衰えを意味するサルコペニアは後期高齢者において有症率が上昇し，身体機能の障害や死亡と強く関連していることが指摘されている。サルコペニアと関連する要因は様々で複雑であるが，不活動や栄養など可変要因の改善に焦点を当てた予防策の効果を検討したところ，骨格筋量の増加，体力の向上には，運動指導，栄養指導ともに有効であった。しかし，サルコペニア高齢者に多く見られる老年症候群の解消には，運動指導がより有効であることを検証した。

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特集：ロコモティブシンドロームと生活習慣病

3．ロコモティブシンドロームの発症メカニズム

4）サルコペニアと ロコモティブシンドローム

Kim Hunkyung
金　憲経

ライフ・サイエンス

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3．ロコモティブシンドロームの発症メカニズム

4）サルコペニアとロコモティブシンドローム

Kim Hunkyung
金　憲経*

*東京都健康長寿医療センター研究所

はじめに

人間の諸機能は，中年期を過ぎると低下ないしは喪失が徐々に増してくる．その背景要因の1つに，体組成の変化が挙げられる．加齢に伴う体組成の変化の中で，最も特徴的なのは脂肪組織量の増加と，骨や骨格筋を含んだ除脂肪組織量（fat-free mass：FFM）の低下である．加齢に伴うFFMの変化は，男性で0.34 kg/yr，女性で0.22 kg/yr減少することが[1]，筋肉量は，男性で0.19 kg/yr，女性で0.11 kg/yr減少するが，50歳代以降では下肢骨格筋量の減少が顕著であることが指摘されている[2]．加齢に伴って筋肉量や骨格筋量が減少すると，筋の質を表す筋力の衰弱をもたらし，特に下肢筋力の衰えは歩行機能を著しく低下させ，ひいては転倒・骨折の原因となるなど，高齢者の移動能力を制限してしまう重大な要因である．

一般的にロコモティブシンドローム（以下，ロコモ）は，運動器の障害のため移動能力の低下を来し要介護状態になっていたり，要介護状態になる危険性の高い状態を指す概念である．身体活動は骨，筋肉，関節，神経などの組織や器官の機能的連合によって産出される結果であり，どれか1つ不具合になっても上手く働かない．

ここでは，ロコモとサルコペニア（sarcopenia）に共通の媒介要因として考えられる筋力の衰えという観点から，ロコモとサルコペニアの関連性や位置づけについて簡単に紹介する．

表1　性・年齢・人種別にみたサルコペニアの有症率

年齢群（歳）	男性 ヒスパニック（n＝221）	男性 白人（n＝205）	女性 ヒスパニック（n＝209）	女性 白人（n＝173）
＜70	16.9	13.5	24.1	23.1
70～74	18.3	19.8	35.1	33.3
75～80	36.4	26.7	35.3	35.9
＞80	57.6	52.6	60.0	43.2

（文献4より引用）

サルコペニアの定義および有症率

加齢に伴って徐々に起こり得る筋肉量の減少や筋力の衰えを表す言葉として「sarcopenia」が1989年以降使用され[3]，老年症候群の発症と深く関わっていることから注目されるようになっている．

現在サルコペニアの操作的定義として広く用いられているものの1つとしては，Baumgartnerらの定義がある．この定義は，二重エネルギーX線吸収法（dual energy x-ray absorptiometry, DXA）から求めた四肢の筋量（appendicular skeletal muscle mass：ASM）を身長（m²）で除したskeletal muscle mass index（SMI）を指標としたものである．サルコペニアの定義は，18～40歳成人のSMI平均より2 SD以下の場合とされている．この定義に基づく有症率は，70歳以下の高齢者で13.5～24.1%の範囲であるが，80歳以上になると43.2～60.0%に上昇する（表1）．さらに，サルコペニアのカットポイントは，SMIが男性で7.26 kh/m²，5.45 kg/m²と

表2　サルコペニア選定に用いた骨格筋量のカットポイント

報告者	筋量の測定法	定　義	男　性	女　性
Baumgartner, et al	DEXA	ASM/Ht², 若年成人2SD↓	7.26	5.45
Tanko, et al	DEXA	ASM/Ht², 若年成人2SD↓	*	5.40
Janssen, et al	BI	SMI	8.50	5.75
Chien, et al	BI	SMI, 若年成人2SD↓	8.87	6.42
Sanada, et al	DEXA	ASM/Ht², 若年成人2SD↓	6.87	5.46

ASM (kg) = appendicular skeletal muscle mass estimated by DXA.
SM (kg) = skeletal muscle mass estimated by BI.
SMI = SM/Ht², Ht = height.
（文献4より引用）

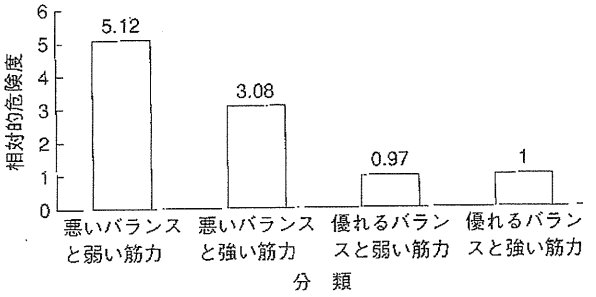

図1　歩行障害の予知因子
（文献5より引用）

提案するとともに，disabilityと密接に関連する（表2）ことから，サルコペニアは高齢期の大きな健康問題としてとらえるべきであると強調している[4]．

歩行機能には筋力とバランスが密接に関わっている

歩行機能は，体力全般の代表的な指標である．外出を楽にし，活動範囲を広げ，元気で長生きを実現するためには，歩行機能の維持・向上は不可欠な要素である．高齢者歩行パターンの特徴は，歩行速度の低下，歩幅の短縮，歩隔の増大，両脚支持時間の延長，遊脚期での足の挙上の低下，腕の振りの減少，不安定な方向転換などである．高齢者に多くみられる歩行機能の低下は，死亡率の上昇，転倒率の増加，生活機能の障害など，様々な指標と密接に関わっていることが多くの研究で指摘されている．

Rantanenらが，65歳以上の高齢女性758名を対象に3年間追跡調査し，歩行障害の発生と関連する要因について検討した結果によれば，「筋力の減少とバランス能力の低下」という条件の対象者は「優れる筋力とバランス機能」を有する対象者に比べて，歩行障害発生の危険性の高いことを指摘し（RR＝5.12，95% CI＝2.68–9.80），歩行機能を維持するためには筋力向上とバランス機能の改善が必要であると強調している（図1）[5]．

サルコペニアの高齢者の特徴

筆者は，大都市部在住の75歳以上の後期高齢女性1,399名を対象に，「四肢の骨格筋量が少ない」「BMIが低い」「膝伸展力が低い」3つの基準に該当する場合をサルコペニアと定義し，該当者304名（21.7%）を抽出し，特徴を調べている．その結果によれば，サルコペニア高齢者は，年齢が高く，下腿三頭筋周囲，BMI，筋肉量は低値を示すとともに健康度自己評価，定期的な運動習慣をもっている者の割合も低いという傾向である．しかし，外出頻度が少ない者の割合は高値を示し，サルコペニアと判定された高齢者は活動量が少なく，自分の健康に対する自信感を喪失している者が多いと推測できる．一方，既往歴においては，貧血症，骨粗鬆症，骨折歴は有意に高い割合を示しているが，高血圧症，脂質異常症は正常群より低い割合を示していることから，サルコペニア高齢者の場合，骨粗鬆症に伴う骨折危険性が高いことが示唆されている（表3）．さらに，サルコペニア高齢者の歩行機能を調べるために，5 mの最大歩行速度を計測し，サルコペニア群と正常群を比較したところ，図2に示した通りに，サルコペニア群は1.58±0.34 m/sec，正常群は1.71±0.36 m/secとして，サルコペニア群の歩行速度が有意に低いことが確認されている[6]．

サルコペニアと関連する要因

老化に伴う筋骨格筋量減少の原因としては，加齢，IGF-1の分泌減少，慢性疾患，アンドロゲン・エストロゲン分泌の減少，炎症性サイトカインの増加，身体活