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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Six-year longitudinal changes in body composition of middle-aged and elderly Japanese: Age and sex differences in appendicular skeletal muscle mass

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Aim: Little is known about longitudinal changes of body composition measured by dual-energy X-ray absorptiometry (DXA) in middle-aged and elderly individuals. We evaluated longitudinal changes of body composition, and age and sex differences in appendicular skeletal muscle mass.

Methods: Participants were 1454 community-dwelling Japanese men and women aged 40–79 years. Body composition at baseline and 6-year follow up was measured by DXA.

Results: Fat increased significantly in men of all ages, and in women aged in their 40s and 50s. Among men, arm lean tissue mass (LTM) changed by 0.9%, –0.5%, –1.4% and –3.7%, respectively, for the 40s to the 70s, and decreased significantly in the 60s and 70s. Leg LTM in men changed by –0.4%, –1.3%, –1.7% and –3.9%, respectively, and decreased significantly from the 50s to the 70s. Compared with the preceding age groups, significant differences were observed between the 60s and 70s in arm and leg LTM change in men. Among women, arm LTM changed by 0.7%, 0.2%, 1.6% and –1.5%, respectively, which was significant in the 60s and 70s. Leg LTM decreased significantly in all age groups of women by –2.0%, –2.8%, –2.4% and –3.9%, respectively. With respect to sex differences, leg LTM loss rates were significantly higher in women than men at the 40s and 50s.

Conclusions: Longitudinal data suggest that arm and leg LTM decreased markedly in men in their 70s, and leg LTM had already decreased in women in their 40s. **Geriatr Gerontol Int 2014; 14: 354–361.**

Keywords: aging, appendicular skeletal mass, body composition, longitudinal study.

Introduction

Significant changes in body composition occur with aging, and these changes greatly affect health and physical function. Cross-sectional studies have suggested that skeletal muscle mass decreases with age,[1–3] and that fat mass increases linearly or curvilinearly with age.[4,5] Sarcopenia, age-associated loss of skeletal muscle mass,[6,7] is correlated with functional impairment and disability.[8,9] In advanced countries, where the elderly population is rapidly growing, the prevention of sarcopenia is important, and changes in appendicular skeletal muscle mass with aging need to be clarified to develop appropriate measures for sarcopenia.

Metter *et al.* reported that the relationship between muscle quality and age is dependent on how muscle is estimated, and on whether subjects are studied cross-sectionally or longitudinally.[10] Most studies dealing with body composition changes with aging have been cross-sectional, and their results might not reflect actual changes with aging. There have been some longitudinal reports of body composition using dual-energy X-ray absorptiometry (DXA)[11–14] or other methods,[15,16] but the number of participants and their age range were limited. With respect to evaluation, previous studies have reported that DXA is an accurate method for measuring body composition.[17–19] To date, there have been no

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large-scale, population-based studies using DXA to evaluate longitudinal changes of body composition from middle age. In the present study, 6-year longitudinal changes in body composition measured by DXA were examined, and sex and age group differences in appendicular skeletal muscle mass changes were evaluated in middle-aged and elderly Japanese individuals.

Methods

Study sample

The data of the present study were collected as part of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). NILS-LSA is a population-based, prospective cohort study of aging and age-related diseases with follow up of the participants every 2 years. Participants in the NILS-LSA were randomly-selected age- and sex-stratified individuals selected from the pool of independent residents in the NILS neighborhood, Obu City and Higashiura Town, Aichi Prefecture, in central Japan. The age at the first wave ranged from 40 to 79 years. Details of the NILS-LSA have been given elsewhere.[20] A total of 2258 men and women took the examination by DXA at the first wave (from April 1998 to March 2000) of NILS-LSA. Among them, a total of 1469 participants (748 men and 706 women) underwent the evaluation by DXA in the fourth wave (from June 2004 to July 2006). We used the data of the participants who attended both investigations. There were various reasons why the participants could not be followed up; for example, transfer to another area, drop out for personal reasons, or death. Participants who used androgen and estrogen drugs were excluded. The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants.

Anthropometric variables

Bodyweight was measured to the nearest 0.1 kg using digital scales, height was measured to the nearest 0.1 cm using a stadiometer, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Body composition

Body composition, fat mass, lean tissue mass (LTM), and bone mineral content (BMC) at baseline and 6-year follow up were assessed by DXA (QDR-4500; Hologic, Madison, OH, USA). LTM is equal to the fat-free mass minus BMC. Arm and leg LTM compartments were examined. Absolute change in each body composition measure was calculated as follow-up value minus baseline value. Percentage of change in each body composition measure was calculated as follows:

$$\text{Percent change} = (\text{absolute change value}/\text{baseline value}) \times 100$$

Total physical activity

Participants responded to a self-administered questionnaire, and were interviewed according to an assessment method for leisure time and on-the-job physical activity within the last 12 months by trained interviewers.[21] Each activity was classified into four categories according to the intensity as determined by metabolic equivalent scores by duration in minutes. The total physical activity score was calculated by summing physical activity scores during leisure time, on the job, sleep and residual time.

Prevalence of diseases and smoking status

Prevalence of diseases (cerebrovascular disease, heart disease and diabetes mellitus) and smoking status at baseline were determined by a questionnaire.

Statistical analysis

Data were analyzed with the Statistical Analysis System (SAS) release 9.13 (SAS Institute, Cary, NC, USA). Differences between baseline and follow-up characteristics were tested using paired *t*-tests. The χ^2-test was carried out to compare smoking status and disease prevalence between men and women. The participants were analyzed by age decade groups (40s, 40–49 years; 50s, 50–59 years; 60s, 60–69 years; 70s, 70–79 years at baseline). Changes in body composition over time in each age group were tested using paired *t*-tests. Sex and age group differences in arm and leg LTM were analyzed using the general linear model (GLM). Another GLM, with adjustment for confounding factors, the presence of diseases (cerebrovascular disease, heart disease and diabetes mellitus), smoking status and total physical activity at baseline, was also evaluated. Values of $P < 0.05$ were considered to show statistical significance.

Results

Mean ages at baseline were 57.2 ± 9.9 years in men and 56.2 ± 9.9 years in women. The mean follow-up interval was 6.3 ± 0.3 years both in men and women. The participants' anthropometric variables, total physical activity, smoking status and prevalence of diseases at baseline are shown in Table 1.

Weight and height were significantly higher in men than women, and there was no difference in BMI. Total

Table 1 Baseline anthropometric variables, total physical activity, and prevalence of smoking status and diseases

	Men	Women
Weight (kg)	63.4 ± 8.4**	53.6 ± 7.5
Height (cm)	165.3 ± 6.0**	152.3 ± 5.5
BMI (kg/m^2)	23.2 ± 2.5	23.1 ± 2.9
Total physical activity (*10^3*METS*min/y)	705.3 ± 93.5**	736.5 ± 68.8
Smoking status (%)		
Never	22.9**	90.5
Past	41.0**	2.6
Current	36.1**	7.0
Prevalence of disease (%)		
Cerebrovascular disease	2.0*	0.7
Heart disease	9.9	7.8
Diabetes mellitus	7.1*	3.1

Values for anthropometric variables and total physical activity are mean ± standard deviation. Differences between men and women were evaluated by *t*-test or χ^2-test. Significantly different from women, $^{**}P < 0.01$, $^{*}P < 0.05$. METS, metabolic equivalents.

physical activity was significantly greater in women than in men. There were significant differences in smoking status, and prevalence of cerebrovascular disease and diabetes between men and women.

Table 2 shows changes in body composition by age groups in men. A significant weight increase was observed from the 40s to 60s age groups, but not for the 70s age group. There were significant increases in fat for all age groups. A significant decrease in BMC was observed in the 70s age group. Total LTM increased in the 40s and 50s age groups, and decreased in the 70s age group. Arm LTM increased in the 40s age group, and decreased in the 60s and 70s age groups. Leg LTM decreased significantly from the 50s to the 70s age group.

Table 3 shows changes in body composition by age groups in women. Significant increases in weight in the 40s and 60s age groups, and in fat in the 40s and 50s age groups were observed. There were significant decreases in BMC in all age groups. Total LTM increased significantly in the 60s age group. Arm LTM increased significantly in the 60s age group and decreased in the 70s age group. Leg LTM decreased significantly in all age groups.

Figure 1 presents the percentage change of arm (a) and leg (b) LTM in men. Percentage changes of arm LTM were 0.9%, –0.5%, –1.4% and –3.7%, respectively. Compared with the preceding age group, there were significant differences between the 40s and 50s age groups ($P < 0.05$), and between the 60s and 70s age groups ($P < 0.01$) in men. When adjusting for confounding factors, the significant difference between the 60s and 70s age groups continued, but that between the 40s and 50s age groups disappeared in men.

Percentage changes of leg LTM in men were –0.4%, –1.3%, –1.7% and –3.9%, respectively. Compared with the preceding age group, there were significant differences between the 60s and the 70s age groups ($P < 0.01$), and this did not change after adjustment for confounding factors.

Figure 2 presents percentage change of arm (a) and leg (a) LTM in women.

Percentage changes of arm LTM were 0.7%, 0.2%, 1.6% and –1.5%, respectively. Compared with the preceding age group, there was a significant difference between the 60s and the 70s age groups ($P < 0.01$) in women, and this did not change after adjustment for confounding factors.

Percentage changes of leg LTM in women were –2.0%, –2.8%, –2.4% and –3.9%, respectively. There were no differences between the adjacent age groups in women.

With respect to sex differences of arm LTM within the same age groups, men in the 60s and 70s age groups had a relatively greater percentage decrease change than women ($P < 0.01$), and when adjusting for confounding factors, the significant differences persisted. With respect to sex differences of leg LTM within the same age groups, women in the 40s and 50s age groups had a significantly greater percentage decrease change than men ($P < 0.01$), and after adjustment for the confounding factors, the significance of these differences did not change.

Discussion

The present study showed the 6-year longitudinal changes in body composition measured by DXA in men

Table 2 Changes in body composition by age group during the 6-year follow-up period in men

	Age group	Baseline (kg)	Change (kg)	*P*-value	Percent change (%)
Weight	40s	66.8 ± 8.5	1.9 ± 3.4	<0.0001	2.7
	50s	64.4 ± 7.7	1.5 ± 3.2	<0.0001	2.4
	60s	61.5 ± 7.8	1.5 ± 3.7	<0.0001	2.6
	70s	58.7 ± 7.7	0.4 ± 3.2	0.15	0.6
Fat	40s	14.1 ± 4.2	1.1 ± 2.2	<0.0001	8.4
	50s	13.4 ± 3.8	1.2 ± 2.2	<0.0001	10.4
	60s	13.5 ± 3.8	1.3 ± 2.4	<0.0001	11.4
	70s	13.0 ± 3.7	1.0 ± 2.1	<0.0001	8.3
BMC	40s	2.37 ± 0.29	−0.01 ± 0.06	0.09	−0.3
	50s	2.31 ± 0.30	−0.01 ± 0.06	0.07	−0.4
	60s	2.18 ± 0.30	−0.01 ± 0.07	0.05	−0.5
	70s	2.08 ± 0.26	−0.04 ± 0.08	<0.0001	−1.9
LTM	40s	50.4 ± 5.4	0.8 ± 1.6	<0.0001	1.6
	50s	48.6 ± 4.8	0.3 ± 1.6	0.002	0.7
	60s	45.8 ± 4.7	0.2 ± 1.8	0.08	0.5
	70s	43.5 ± 4.8	−0.5 ± 1.8	0.003	−1.3
Arm LTM	40s	5.97 ± 0.75	0.05 ± 0.34	0.03	0.9
	50s	5.73 ± 0.69	−0.04 ± 0.31	0.08	−0.5
	60s	5.35 ± 0.67	−0.08 ± 0.29	0.0002	−1.4
	70s	5.01 ± 0.67	−0.18 ± 0.30	<0.0001	−3.7
Leg LTM	40s	15.89 ± 1.97	−0.05 ± 0.74	0.32	−0.4
	50s	15.08 ± 1.82	−0.21 ± 0.79	<0.0001	−1.3
	60s	14.14 ± 1.69	−0.25 ± 0.89	<0.0001	−1.7
	70s	13.45 ± 1.81	−0.52 ± 0.73	<0.0001	−3.9

$n = 204$ in age group 40s, $n = 234$ in age group 50s, $n = 196$ in age group 60s, $n = 114$ in age group 70s. Values of baseline and change are mean ± standard deviation). Significant changes from baseline were evaluated by paired *t*-test. BMC, bone mineral content; LTM, lean tissue mass.

and women aged 40–79 years. Weight and fat mass increased or did not change in both men and women in all age groups. Among men, marked decreases in both arm and leg LTM were found in the 70s age group. Among women, leg LTM decreased significantly in all age groups. The rates of loss in arm LTM were larger in men than in women in the 60s and 70s, the elderly age groups. In contrast, the rate of loss in leg LTM was larger in women than in men in the 40s and 50s, the early stage, middle-aged groups.

Previous cross-sectional studies suggested that appendicular skeletal muscle mass decreases with age in both sexes.[1,3,22] However, these cross-sectional studies show indirect evidence of age-related changes.[23] There have been several longitudinal studies of body composition measured by DXA. Gallagher *et al.* reported that there were significant decreases in leg skeletal muscle mass, and tendencies for a loss of arm skeletal muscle mass in healthy men and women aged over 60 years during an average 4.7-year follow up.[13] Visser *et al.* showed that, over a 2-year period, appendicular skeletal muscle mass decreased −0.8% in men, but not in women aged 70–79 years, and leg lean soft tissue mass decreased significantly in both sexes.[12] Zamboni *et al.* found that significant losses of leg skeletal muscle were observed in stable-weight, elderly (68–78 years) men and women over a 2-year period.[13] However, in most of these studies, the participants were aged over 60 years. In the present study, we showed the changes in body composition in participants of a wide age range, 40–79 years. In the 60s and 70s age groups, except for the arm LTM in the 60s age group in women, there were significant decreases of arm and leg LTM in men and women. Already in the 40s and 50s age group, there were significant decreases in leg LTM in women.

With respect to sex differences, previous cross-sectional[1,5] and longitudinal studies[11,13,14] reported that the rates of decrease in appendicular lean mass were greater for men than for women. The present study showed that the rates of loss in arm LTM were greater in men than in women in the 60s and 70s age groups. However, the rate of loss in leg LTM was greater in women than in men in the 40s and 50s age groups, and no significant sex difference was found in the 60s and 70s age groups. Previous longitudinal studies evaluated the differences using absolute change,[11,12,14] whereas the

Table 3 Changes in body composition by age group during the 6-year follow-up period in women

	Age group	Baseline (kg)	Change (kg)	*P*-value	Percent change (%)
Weight	40s	54.8 ± 7.9	1.2 ± 3.9	<0.0001	2.1
	50s	54.4 ± 6.9	0.3 ± 3.0	0.19	0.5
	60s	53.3 ± 7.1	0.5 ± 2.8	0.02	0.9
	70s	49.9 ± 7.8	−0.2 ± 3.1	0.60	−0.4
Fat	40s	16.5 ± 4.6	1.2 ± 2.6	<0.0001	8.0
	50s	17.2 ± 4.4	0.5 ± 2.3	0.001	3.6
	60s	17.7 ± 4.5	0.3 ± 2.0	0.06	2.1
	70s	16.2 ± 4.7	0.02 ± 2.3	0.95	0.5
BMC	40s	1.98 ± 0.25	−0.11 ± 0.13	<0.0001	−5.6
	50s	1.77 ± 0.26	−0.13 ± 0.10	<0.0001	−3.7
	60s	1.54 ± 0.23	−0.06 ± 0.06	<0.0001	−3.7
	70s	1.36 ± 0.23	−0.06 ± 0.06	<0.0001	−4.4
LTM	40s	36.3 ± 4.2	0.1 ± 1.8	0.24	0.3
	50s	35.5 ± 3.4	−0.1 ± 1.3	0.18	−0.3
	60s	34.0 ± 3.5	0.2 ± 1.2	0.008	0.7
	70s	32.4 ± 3.8	−0.1 ± 1.2	0.34	−0.4
Arm LTM	40s	3.56 ± 0.54	0.02 ± 0.28	0.22	0.7
	50s	3.53 ± 0.44	0.003 ± 0.22	0.85	0.2
	60s	3.43 ± 0.45	0.05 ± 0.23	0.003	1.6
	70s	3.24 ± 0.47	−0.05 ± 0.20	0.02	−1.5
Leg LTM	40s	11.19 ± 1.64	−0.22 ± 0.63	<0.0001	−2.0
	50s	10.88 ± 1.34	−0.31 ± 0.57	<0.0001	−2.8
	60s	10.42 ± 1.33	−0.25 ± 0.48	<0.0001	−2.4
	70s	9.91 ± 1.36	−0.39 ± 0.51	<0.0001	−3.9

$n = 216$ in age group 40, $n = 218$ in age group 50, $n = 177$ in age group 60, $n = 95$ in age group 70. Values of baseline and change are mean ± SD (standard deviation). Significant changes from baseline were evaluated by paired t-test. BMC, bone mineral content; LTM, lean tissue mass.

present study used a relative index, the percent change. In the present study, comparisons using the absolute change in mass were also made, but the results for the sex differences showed almost the same tendency (data not shown). As there were many differences among the studies in the participants' characteristics, race, lifestyle and study design, further examination is required to clarify these differences.

The present study showed that there were significant decreases in leg LTM, but not in arm LTM, among women in the 40s to 60s age groups. Lynch *et al.* reported that, with increasing age, leg muscle quality declined ~20% more than arm muscle quality in women.[24] Based on these results, changes in muscle mass or function might differ between arms and leg muscles in women; decreases were apparent in the leg muscles. Leg muscle mass is closely associated with functional performance[14,25] and, in general, women have significantly less skeletal muscle mass than men.[1,2,23] There were several reports that frailty was higher in women than men in the elderly.[26,27] Therefore, it might be especially important for women to prevent the decrease of leg LTM from middle age. Some studies have suggested the relationship between menopause and loss of muscle mass,[28–30] and that estrone predicted loss of appendicular muscle mass.[31] The early onset of leg LTM decrease of women in the present study might be associated with the menopausal transition.

For evaluating sarcopenia, skeletal muscle mass index (SMI), obtained by dividing appendicular skeletal muscle mass by height squared, is often used.[8] Appendicular skeletal muscle mass was measured as the sum of the LTM for arms and legs. In the present study, both arm and leg LTM significantly decreased at the same time in the 70s age group in men. In contrast, in women, the time of LTM decrease differs in arms and legs. Therefore, in order to evaluate the decrease of muscle mass in women more clearly, it might be better to use leg LTM alone. Further detailed analyses of LTM in women would be necessary in future studies.

Regarding fat mass change, Hughes *et al.* reported that fat mass increased in the elderly, but the increase in women was attenuated with advancing age.[15] Other studies showed that fat mass increased significantly in elderly men and decreased non-significantly in elderly women.[11,12] As in these previous studies, the present

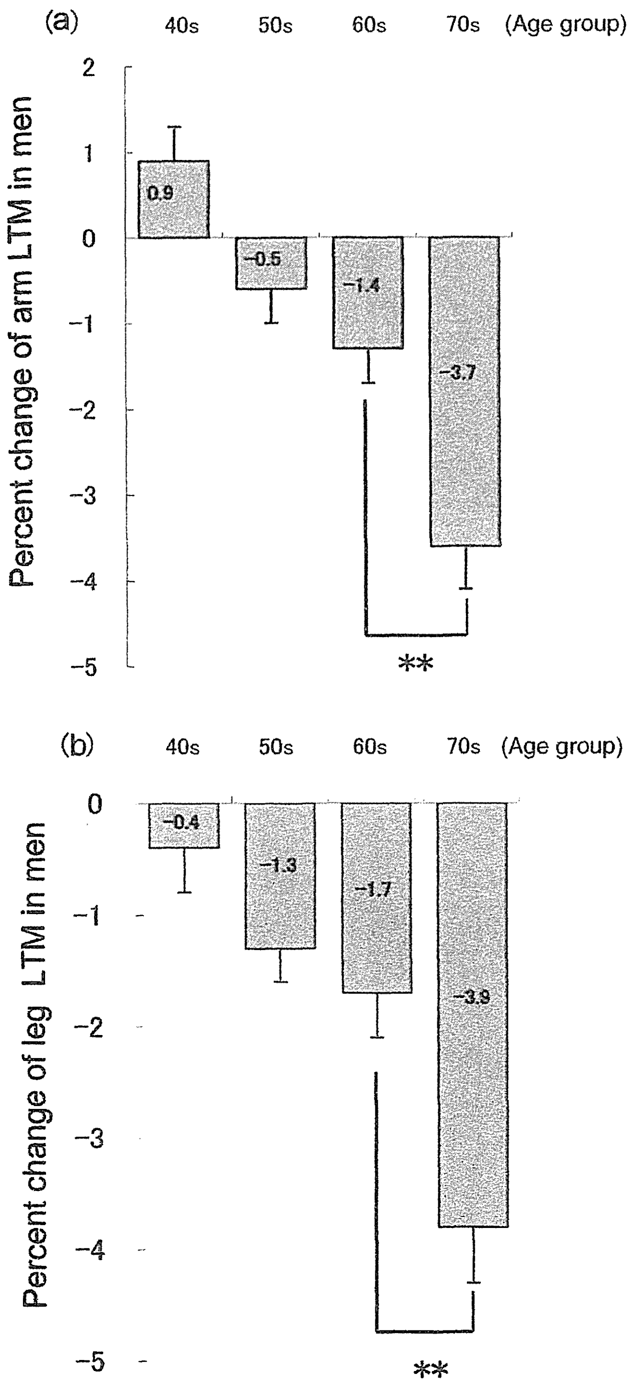

Figure 1 Percentage change of (a) arm and (b) leg lean tissue mass (LTM) during the 6-year follow-up period by age group in men. Values are mean ± standard error of the mean. $^{**}P < 0.01$, compared with the preceding age group adjusting for confounding factors.

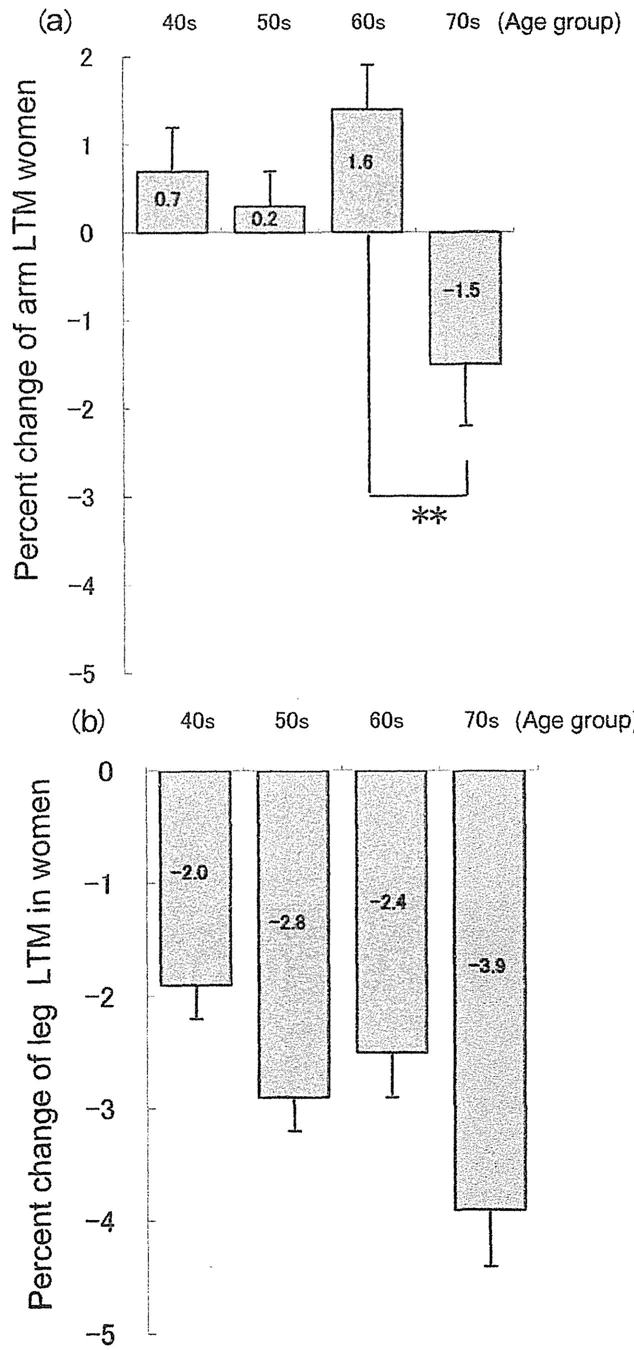

Figure 2 Percentage change of (a) arm and (b) leg lean tissue mass (LTM) during the 6-year follow-up period by age group in women. Values are mean ± standard error of the mean. $^{**}P < 0.01$, compared with the preceding age group adjusting for confounding factors.

study showed that fat mass increased in all age groups in men and that, in women, it increased in the 40s and 50s, but it did not change thereafter.

The strengths of the present study are the large age- and sex-stratified sample size, the wide range of ages and the 6-year follow-up period. This is the first study to report the longitudinal changes of body composition, measured by DXA in 40- to 79-year-old Japanese subjects. With respect to race, so far, no longitudinal study of Asians has been reported, and there has not been sufficient research on racial differences. It will be necessary to clarify racial differences and consider various environmental factors in future studies.

Although loss of muscle mass is associated with decline in strength[32,33] and disability,[8] there were reports that strength decline in older adults is much more rapid than loss of muscle mass,[32] and that muscle strength is more important than muscle mass in estimating mortality risk.[9,34,35] Recently, the European Working Group on Sarcopenia in Older People recommended that the presence of both low muscle mass and low muscle function (strength or performance) be used.[36] Thus, to measure not only muscle mass, but also muscle strength, might be important for the evaluation of actual activity, especially in the elderly.

As several reports have suggested differences of bodyweight and the prevalence of obesity by birth cohort,[37,38] there might also be differences of changes in body composition by birth cohort. In addition, although the participants of the present study were randomly selected, they were relatively well-functioning men and women able to participate in the study. Therefore, the results might not accurately represent changes with aging in the general population.

In conclusion, we evaluated 6-year longitudinal changes of body composition in middle-aged and elderly participants. Remarkable decreases of arm and leg LTM in men in the 70s age group, and early decreases of leg skeletal muscle mass already in the 40s age group in women were found. We believe that these results might offer important information with respect to prevention of sarcopenia, and improving the health-related quality of life in older adults.

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Disclosure statement

The authors declare no conflict of interest.

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第20回日本未病システム学会学術総会
■プロシーディング 14

地域在住中高年者のプロリン摂取量が知能に及ぼす影響に関する縦断的研究

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要 約

【目的】本研究では，地域在住中高年者を対象とし，知能の10年間の経年変化，特に知識量に着目しプロリン摂取量，年齢が及ぼす影響を明らかにすることを目的とした．

【方法】対象者は「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」の第2次調査に参加した中高年者2,024名（男性1,031名，女性993名，40－81歳）．その後，約2年間隔で行なわれた全5回の追跡調査で測定した知能得点（WAIS-R-SF「知識」得点）を目的変数とし，プロリン摂取量（g/1,000kcal/日：3日間の食事記録調査より推定），第2次調査からの経過年数，年齢の主効果，プロリン摂取量×年齢，プロリン摂取量×経過年数，プロリン摂取量×年齢×経過年数の交互作用項，調整変数（BMI，抑うつ）を固定効果とし，個人の切片と傾きを変量効果とする線形混合効果モデルを用いて性別に検討した．

【結果】プロリン摂取量と経過年数の交互作用項に着目したところ，男女ともに動物性食品からのプロリン摂取量×年齢×経過年数の交互作用が有意であった（$p<0.0001$）．10年間の知識得点の推移は，男女とも40，50歳で，動物性プロリンの多摂取群と少摂取群との傾きの差が有意であり，多摂取群の知識得点がより増加していたが，60，70歳では，傾きに有意な差は認められなかった．女性の60，70歳では，プロリン多摂取群で高い得点を維持していた．一方，植物性食品由来のプロリンでは知識得点と有意な関連はなかった．

【考察および結論】本研究で検討したプロリンは，動物性と植物性で知識得点に与える影響が異なっており，体内での利用効率や動態が異なることが示唆された．男女ともに中年者では動物性プロリンを多く摂取すると知識の獲得および維持に有効である可能性が示され，さらに，女性では高齢でも動物性食品よりプロリンを多く摂取することにより高い得点を維持していた．

Key words　プロリン摂取量，知識量，一般地域住民，長期縦断研究，動物性食品

1 目 的

高齢期の知的能力を維持することは，高齢者のQOLを支えるだけでなく社会保障や介護の負担の軽減に繋がる重要な課題である．基礎研究より，肉類や魚介類，乳製品に多く含まれるアミノ酸であるプロリンが，アルツハイマー病のミトコンドリア機能障害や細胞アポトーシスを防ぐ可能性が報告されている[1]が，一般住民の日常的に摂取するプロリンの量や食品群別寄与率，プロリンと知能との関連は不明である．そこで本研究では，地域在住中高年者の知的能力，特に知識量に着目し，10年間の長期縦断データを用いて，プロリン摂取量，年齢がその後の知能の経時変化にどのような影響を及ぼすかを明らかにすることを目的とした．

2 方 法

1) 対象者

対象者は「国立長寿医療研究センター・老化に関する長期縦断疫学研究（National Institute for Longevity Sciences – Longitudinal Study of Aging : NILS-LSA）」[2,3]の第2次調査（2000-02年，以後ベースライン）に参加し，その後，約2年間隔で行なわれた第3次調査（2002-04年）から第7次調査（2010-12年）までの全5回の追跡

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調査に1回以上参加した地域在住中高年者である.

本研究ではベースライン時参加者2,259名のうち，認知障害を有する可能性のある者を除外し(MMSE≦23)，下記の検査を完了した2,024名（40～81歳：男性1,031名，女性993名）ののべ9,463件のデータを用いた.

尚，NILS-LSAは年齢および性で層化無作為抽出された地域住民を対象とした縦断的コホート調査であり，国立長寿医療研究センター倫理委員会の承認を得た後，事前に説明会を行い，文書による同意の得られた者を対象とし行われている.

2)ベースライン時のプロリン摂取量

独自に構築した「NILS食品アミノ酸成分表2010」[4]を用いて，ベースラインでの3日間食事秤量記録調査[5]結果から，摂取エネルギー1,000kcalあたりの動物性プロリン，植物性プロリンの一日平均摂取量（g/1,000kcal/日）を推定した.

3)知識量(ベースライン，および各追跡調査時)

ウェクスラー成人知能検査改訂版[6]（Wechsler Adult Intelligence Scale-Revised ：WAIS-R）簡易実施法下位尺度の「知識（得点範囲 0～29，一般的な知識量の指標)」を用いた.

4)その他の調整項目(ベースライン時)

調整変数として，Body Mass Index（BMI: kg/m^2），抑うつ検査得点，教育年数をモデルに投入した．BMIは，身長，体重の測定値より算出した．抑うつ検査には，CES-D（Center for Epidemiologic Studies Depression Scale；20項目，4尺度，得点範囲0-60点）を用いた．教育年数は自記式質問票により回答を得た.

5)解析方法

プロリン摂取量が知能に及ぼす影響に着目し，ベースラインおよび各追跡調査時に測定した「知識」得点を目的変数とし，個人の切片と傾きを変量効果とする線形混合効果モデルにおいて，固定効果の異なる3つのモデルで性別に検討した．モデル1では，動物性または植物性プロリンの一日平均摂取量（g/1,000kcal/日），ベースライン調査からの経過年数，ベースライン調査時の年齢，BMI，CES-D得点を投入し，モデル2ではモデル1に教育年数を加え，モデル3ではモデル2に交互作用項としてプロリン摂取量×年齢，プロリン摂取量×経過年数，プロリン摂取量×年齢×経過年数を投入した.

解析には，SAS9.3を用い，有意水準は5%とした.

3　結果

表1にベースライン時の対象者特性および平均参加回数，平均最終追跡年数を示した．線形混合効果モデルでの解析結果を表2に示す.

モデル1において，男女ともに「知識」得点の経年変化に対して動物性プロリン摂取量では有意な主効果を示したが，植物性プロリン摂取量では有意な関連はなかった（表2)．モデル2では，「知識」得点と有意な関連があった動物性プロリン摂取量の回帰式に，教育年数を投入した．男性では，プロリン摂取量および年齢の主効果の有意性が消失した．女性ではプロリン摂取量の主効果は有意であったが，年齢の主効果は消失した．交互作用項を投入したモデル3では，男女ともに動物性プロリン摂取量×経過年数および動物性プロリン摂取量×年齢×経過年数の交互作用が有意であった（$p<0.0001$)．すなわち，10年間の「知識」得点の推移に対して，動物性プロリン摂取量の与える影響は経過年数や年齢によって異なることが示された．そこで，「知識」得点の経年変化の推計値を算出するため，モデル3の回帰式に，動物性プロリン摂取量の平均+1SD値を多摂取群，平均-1SDを少摂取群とした摂取量の多寡とベースライン時の各年齢（40，50，60，70歳）を代入し，ベースライン時と10年後の「知識」の得点を推計した（図1)．調整変数には平均値を代入した.

「知識」得点の10年間の推計値から，男性の40, 50歳では，動物性プロリン多摂取群と少摂取群との傾きの差が有意であり，多摂取群の「知識」得点がより増加していた．女性でも40, 50歳で，同様に両者の傾きに有意差がみられた．男女ともに60, 70歳では，傾きに有意差は認められなかった．女性では，60, 70歳においてプロリン多摂取群が高い得点を維持していた.

一方，植物性食品由来のプロリンでは「知識」得点と有意な関連はみられなかった.

4　考察および結論

本研究で検討したプロリンは，動物性食品より多く摂取することにより10年間で「知識」得点をより増加させた．動物性と植物性食品由来のプロリンでは，「知識」得点の経年変化に与える影響が異なっていた．この結果から，プロリン単体の効果ではなく，食品や代謝産物に含ま

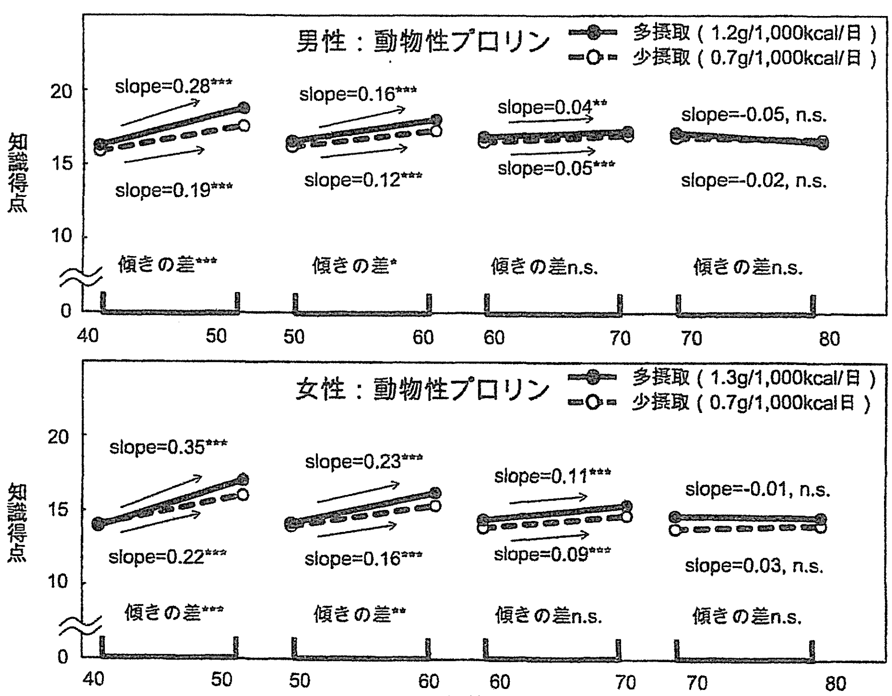
❑ 表1 ベースライン時の対象者の特性

		男性 n=1,031	女性 n=993
年齢群	人数(%)		
40～49歳		249 (24.2%)	238 (24.0%)
50～59歳		269 (26.1%)	267 (26.9%)
60～69歳		265 (25.7%)	253 (25.5%)
70～81歳		248 (24.0%)	235 (23.6%)
年齢	歳	59.3 ± 11.3	59.5 ± 11.1
身長	cm	165.1 ± 6.5	151.9 ± 6.0
体重	kg	63.1 ± 9.4	52.6 ± 8.1
BMI	kg/m^2	23.1 ± 2.8	22.8 ± 3.2
教育歴	年	12.4 ± 2.9	11.5 ± 2.5
CES-D		7.2 ± 6.5	7.5 ± 6.9
栄養素等摂取量（1日平均摂取量）			
エネルギー	kcal	2,292 ± 392	1,868 ± 327
たんぱく質	g	86.5 ± 16.3	72.8 ± 14.1
動物性たんぱく質	g	46.4 ± 13.5	38.1 ± 11.1
脂質	g	59.6 ± 16.6	52.6 ± 15.1
動物性脂質	g	30.0 ± 11.6	25.2 ± 9.9
炭水化物	g	317.2 ± 62.4	268.5 ± 52.9
ナトリウム	g	4736 ± 1099	4057 ± 911
動物性プロリン	g/1,000kcal	0.96 ± 0.25	1.02 ± 0.29
植物性プロリン	g/1,000kcal	1.06 ± 0.22	1.16 ± 0.24
ウェクスラー成人知能検査改訂版			
推定IQ		109 ± 13	105 ± 13
下位検査得点			
知識		16.6 ± 5.2	13.9 ± 5.5
類似		14.5 ± 5.4	13.6 ± 5.3
絵画完成		12.1 ± 3.1	10.9 ± 3.7
符号		53.4 ± 15.1	54.3 ± 16.3
平均参加回数		4.69 ± 1.78	4.67 ± 1.79
平均最終追跡期間		7.81 ± 3.64	7.77 ± 3.67

❑ 表2 プロリン摂取が知能の経年変化に及ぼす影響：線形混合効果モデルの結果

			動物性プロリンでの解析						植物性プロリンでの解析†	
			モデル1		モデル2		モデル3		モデル1	
	固定効果		F値	p値	F値	p値	F値	p値	F値	p値
男性	ベースライン時のプロリン摂取量		4.94	0.0264	1.67	0.1961	0.03	0.8521	0.00	0.9502
	ベースラインからの経過年数		55.65	<.0001	55.35	<.0001	2.67	0.1029	55.71	<.0001
	ベースライン時の年齢		62.85	<.0001	0.00	0.9628	0.29	0.5895	61.01	<.0001
	調整変数	BMI	1.68	0.1956	0.27	0.6009	0.34	0.5578	1.84	0.1748
		CES-D	11.87	0.0006	10.56	0.0012	6.07	0.0138	11.97	0.0005
		教育年数			420.92	<.0001	420.06	<.0001		
	プロリン摂取量 × 経過年数						71.52	<.0001		
	プロリン摂取量 × 年齢						0.00	0.9498		
	プロリン摂取量 × 経過年数 × 年齢						107.23	<.0001		
女性	ベースライン時のプロリン摂取量		8.65	0.0033	4.80	0.0285	1.47	0.226	0.82	0.3652
	ベースラインからの経過年数		117.80	<.0001	117.45	<.0001	2.64	0.1045	117.49	<.0001
	ベースライン時の年齢		88.27	<.0001	1.72	0.1903	2.54	0.1109	84.77	<.0001
	調整変数	BMI	6.55	0.0105	5.03	0.025	4.92	0.0266	6.22	0.0127
		CES-D	6.90	0.0087	6.69	0.0097	4.39	0.0362	6.75	0.0094
		教育年数			181.67	<.0001	181.44	<.0001		
	プロリン摂取量 × 経過年数						59.04	<.0001		
	プロリン摂取量 × 年齢						2.58	0.1081		
	プロリン摂取量 × 経過年数 × 年齢						71.69	<.0001		

†：植物性プロリン摂取量の主効果は，モデル1の解析方法においても「知識」得点に対して有意な影響が認められなかった．そのため，それ以降のモデルでの検討を行わなかった．



(*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, n.s.: not significant)

❑ 図1 動物性プロリン摂取量の違いでの「知識」得点推計値の10年間の経年変化（上段：男性，下段：女性）

線形混合効果モデルを用いて推定した．

モデル3の回帰式にプロリンは「平均±1SD値」の2値を，年齢はベースライン時40, 50, 60, 70歳の年齢，経過年数はベースラインと10年を代入し，2時点の知能の得点を推計した．

れる生体機能を有するプロリン含有ペプチドの種類や量が，動物性と植物性食品で異なるためと推測した．ヒトでのジペプチド，トリペプチドの吸収メカニズムが明らかになりつつあり[7]，生体機能を有するトリペプチドの効果が期待されている．例えば，乳製品に含まれるラクトトリペプチド（プロリン2分子含有）はACEの働きを阻害し，血圧上昇を抑制する[8]特定保健用食品として承認されている．血管病変の進展抑制は認知症予防と関連することが示されており，認知機能の低下抑制への貢献が期待される．また，コラーゲンペプチドもプロリンやヒドロキシプロリンなどを多く含んでいる．このペプチド（Pro-Hyp）は生体内で線維芽細胞の増殖に関与しているとの報告[9]があり，脳神経，特に海馬神経の修復，形成による認知機能維持の可能性がある．

副解析として，同モデルに動物性食品摂取量（g/1,000 kcal/日）を主効果として投入し「知識」得点への影響を検討したところ，有意な関連は認められなかった．このことからも，プロリン含有ペプチドを特異的に含む牛乳やコラーゲンなどの摂取が，中高年期の知識の獲得・維持に有効である可能性が示唆された．

プロリンは，体内で合成されるため非必須アミノ酸に分類されているが，プロリン含有ペプチドは特定の食品にのみ含まれている可能性があり，たんぱく質合成のためのアミノ酸供給源としてだけでなく，特定の生理作用を有する分子として食事から摂取する必要があると考えられる．

しかし，今回の解析では，動物性プロリンを多く含む食品に含まれる他の栄養成分や他因子の関与について否定できない．さらに，「NILS食品アミノ酸成分表2010」はたんぱく質摂取量の94.5%をアミノ酸摂取量で説明する事が可能であるが，アメリカの農務省（USDA: United States Department of Agriculture）の食品成分値のデータや改訂日本食品アミノ酸組成表（昭和61年公表）の古いデータを一部転載していること，置き換え法を用いていることなどから，真のアミノ酸摂取量を推定するには限界がある．また，成分表に記載されているアミノ酸含有量は，季節変動や産地などを考慮したものではないため，推定される摂取量は誤差を含むことも考慮すべきである．

結論として，本研究では，男女ともに中年期に動物性プロリンを多く摂取すると知識の獲得および維持に有効である可能性が示された．さらに，女性では高齢でも動物性食品よりプロリンを多く摂取することにより高い得点を維持していた．

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Longitudinal study of effects of proline intake on intellectual decline in community-dwelling middle-aged and elderly Japanese subjects

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The aim of this study was to elucidate the effect of proline intake and age on age-related changes in intelligence (amount of knowledge) over a 10-year period.

Subjects comprised a total of 2,024 middle-aged and elderly individuals (1,031 men, 993 women; 40-81 years) who participated in the 2nd survey (baseline) of the "National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA)" as well as at least one of the five follow-up surveys until the 7th survey. Animal- and plant-derived proline intakes (g/1,000 kcal/day) was estimated based on the 3-day dietary records at baseline. The amount of knowledge at baseline and follow-up survey was determined using the "Information" subscale of the Wechsler Adult Intelligence Scale-Revised short form (WAIS-R-SF). Using the "Information" score at each point as the objective variable, the effects of proline intake, the years from baseline, age at baseline, their interaction terms, and moderator variables (BMI, CES-D score) were investigated by sex using a linear mixed-effects model.

As for changes in "Information" score over the 10-year period, significant differences in slope were seen between the high and low animal proline intake groups at ages 40 and 50 in both sexes, with the scores increasing more greatly in the high animal proline intake group. Women aged 60 and 70 who were in the high proline intake group had maintained high scores. On the other hand, no significant relationships were observed between plant-derived proline intake and "Information" score.

Proline exerts different effects on "Information" score depending on whether it is derived from animals or plants.

Key words　proline intake, intelligence, community-dwelling, longitudinal study, animal food

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膝関節の変形および痛みと身体組成との関連

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加藤友紀[2)]　大塚　礼[2)]　安藤富士子[2,4)]　下方浩史[2,5)]

はじめに

変形性膝関節症（膝 OA）は，高齢期に QOL や身体機能低下をきたす原因となる運動器疾患の一つである。膝 OA の痛みの増悪因子として肥満はよく知られているが，DXA などによる身体組成を含めた詳細な検討は少ない。そこで，膝関節変形ならびに痛みと身体組成の関連を明らかにするため，地域在住中高年者対象の大規模コホートにて検討を行った。

1　対象および方法

「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」[1)]の第 5 次調査（2006～2008 年）に参加した男女 2,337 名（平均年齢 60.7±12. 6 歳，男性 1,185 名，女性 1,192 名）の 4,750 膝を対象とした。本研究参加者は愛知県大府市および東浦町の 40 歳以上の一般住民から無作為に抽出し選定した。調査項目として，膝関節変形は左右別のエックス線膝荷重位正面像について Kellgren-Lawrence 分類を基に 5 段階に分類し，0～I 度を正常，II 度を軽度変形，III～IV度を重度変形と 3 群に分類し，調査票にて現在の膝関節痛の有無を左右別に調査した。さらに身体組成の指標として Hologic 社製 QDR 4500 を用いて，DXA 法にて下肢脂肪量，下肢筋肉量を測定し，下肢脂肪率（＝下肢脂肪量/体重×100），下肢筋肉率（＝下肢筋肉量/体重×100），下肢筋肉量と下肢脂肪量の比（＝下肢筋肉量/下肢脂肪量），のそれぞれを左右別に算出し，変形の程度により各指標に差があるかどうかについて，男女別および痛みの有無別に検討した。統計解析は一般線形モデルを用い，左右の膝を合わせ年齢を調整した多重比較（Tukey-Kramer 法）により SAS 9.1.3 にて行った。研究は当センターの倫理委員会の承認のもと，紙面での参加者の同意を得て施行した。

2　結　　果

対象の特性を表 1 に示す。男女別および痛みの有無別に，膝関節変形の程度による各指標を比較した結果は，以下のとおりであった。

男性においては，痛みのある例では下肢脂肪率は正常に比べ重度変形で有意に高く（$p < 0.05$），下肢筋肉率，下肢筋肉量と下肢脂肪量の比は，ともに正常に比べ重度変形で有意に低かった（各 $p < 0.05$，図 1A）。一方痛みのない例では下肢脂肪率，下肢筋肉率，下肢の脂肪量と筋肉量の比はいずれも各群間に有意差はなかった（図 1B）。女性では，痛みのある例では下肢脂肪率，下肢筋肉率，下肢筋肉量と下肢脂肪量の比のいずれも各群間に有意差はなかったが，下肢筋肉率は重度変形が軽度変形より低い傾向（$p = 0.053$）があった（図 1C）。一方痛みのない例では，下肢脂肪率は正常に比べ軽度変形で有意に

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表1　対象の特性

	男性（n＝1185）	女性（n＝1192）
年齢（歳）	60.6±12.5	60.8±12.7
身長（cm）	166.0±6.6	152.6±6.2
体重（kg）	64.1±9.3	52.5±8.6
総膝関節数（膝）	2368	2382
エックス線変形程度別の膝関節数		
正常（痛みのある膝%）	1524（7.5）	1300（10.5）
軽度変形（痛みのある膝%）	765（11.5）	859（20.7）
重度変形（痛みのある膝%）	79（50.6）	223（57.0）
BMI（kg/m^2）	23.2±2.7	22.5±3.3
下肢脂肪量（kg）	2.1±0.6	2.8±0.8
下肢筋肉量（kg）	7.4±1.2	5.2±0.8
下肢脂肪率（%）	3.3±0.6	5.3±1.0
下肢筋肉率（%）	11.6±0.9	10.0±0.9
下肢筋肉量と脂肪量の比	3.7±1.1	2.0±0.5

平均±SD

高く（$p<0.05$），下肢筋肉率では各群間に有意差はなかったが，下肢筋肉量と下肢脂肪量の比は正常に比べ軽度変形で有意に低かった（$p<0.01$，図1D）。

3　考　　察

膝 OA の増悪因子として肥満はよく知られているが，DXA などによる身体組成を含めた詳細な検討は多くなく，これまでの国内外における報告のほとんどは女性についての検討である。わが国では，DXA 法を用いた膝 OA 例女性30名と健常女性50名の比較で，体脂肪率は膝 OA 例のほうが健常群より大きかったが，除脂肪量は両群に有意な差を認めなかったとする報告[2]や，Bioelectrical impedance 法を用いた，下肢除脂肪率が膝 OA 群で正常群より低かったとする戸田らの報告[3]，年齢，BMI，腰椎骨密度が一致した対照群との比較で，下肢除脂肪量は膝 OA 群で有意に低下し，脂肪量は有意差がなく，膝 OA 群で進行度の高い側の脂肪量は低い側に比べ有意に高かったとする報告[4]がある。また海外においても，DXA 法で体脂肪量，体脂肪率，体筋肉量は膝 OA 群のほうが正常群より高かったが，体筋肉率は膝 OA 群のほうが低かったとする Johnston Country Osteoarthritis Project での報告[5]や，Bioelectrical impedance 法を用いた，体除脂肪量は MRI 計測での脛骨軟骨量と正，軟骨欠損と負の関連があり，体脂肪量は脛骨軟骨量と負の関連があったとする報告[6]，あるいは，骨格筋量はエックス線関節裂隙幅と正の関連があったが，脂肪量とは一定の関連を認めなかった[7]など，本報告と同様の報告がある。しかしながら，性別や痛みの有無別に行った検討は，渉猟したかぎりこれまでにはなかった。われわれの検討では正常例との比較において，男性では痛みのある例にて重度変形例で下肢の脂肪の割合が高く筋肉の割合が低く，一方女性では痛みのない例にて軽度変形例で脂肪の割合が高く筋肉の割合が低くなっていた。

ま と め

地域在住中高年者を対象とした大規模コホートにて，膝関節の変形と身体組成との関連を検討した。両者の関連は，痛みの有無を考慮した

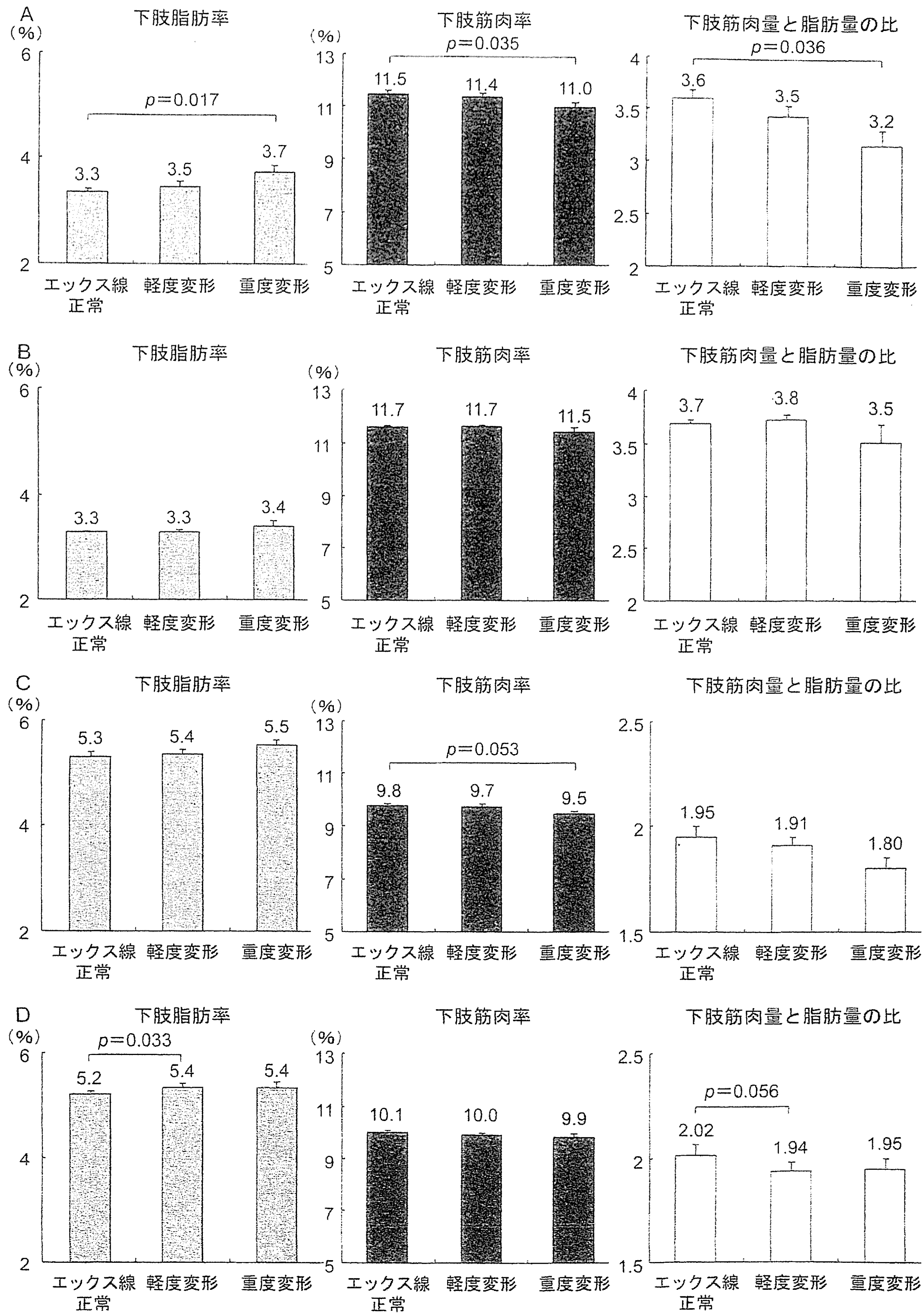

図 1　エックス線膝変形の程度による各指標の比較

年齢を調整した多重比較（Tukey-Kramer 法）にて

A：痛みのある男性例，B：痛みのない男性例，C：痛みのある女性例，D：痛みのない女性例

場合，男女で異なっていた。

【C O I】本演題に関連して，筆頭著者に開示すべき利益相反はありません。

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