Table 2
Femur volume.

	Total volume (cm^3)		Cortical volume (cm^3)		Cancellous volume (cm^3)		Trabecular volume (cm^3)	
Cont.	0.493 ± 0.010	##	0.367 ± 0.007	#	0.126 ± 0.004	##	0.090 ± 0.003	#
PK	0.507 ± 0.010		0.380 ± 0.006		0.127 ± 0.005		0.098 ± 0.005	
MK	0.533 ± 0.008		0.393 ± 0.005		0.141 ± 0.005		0.105 ± 0.005	

Each value represents mean ± S.E.
#: Significant difference between the value of the control group and the MK group (#: $p<0.05$, ##: $p<0.01$).

Biochemical analysis of serum parameters

There were no significant differences in the levels of serum total protein, calcium, inorganic phosphorus, ALP, NTx, GH, IGF-1, IGFBP-3, and glucose among the three groups (Tables 4 and 5, Fig. 4A). Interestingly, the levels of serum triglycerides were significantly lower in PK and MK groups than in the Cont. group ($p<0.05$ and $p<0.01$, respectively) (Fig. 4B). In addition, the level of serum total cholesterol was significantly lower in the MK group than in the Cont. group ($p<0.05$).

Discussion

We compared the effect of PK or MK-4 on BMD, bone strength, fat accumulation, and serum parameters *in vivo*. The total BMC and BMD of the femur were significantly increased after 82 days on the PK compared to the Cont. diet ($p<0.05$, respectively) (Table 3 and Fig. 2A). As shown in Tables 1 and 2, the width, dry or ash weight, and total volume of the femur in the MK group were significantly higher than those of the control group ($p<0.05$, $p<0.05$ and $p<0.001$, respectively). Further, significant increases in the BMC, minimum moment of inertia of cross-sectional areas, and polar moment of inertia of cross-sectional areas of femur were observed in the MK group ($p<0.05$, respectively) (Table 3 and Figs. 2B and C).

In the present study, we revealed the different effects of PK or MK-4 on femoral bone parameters (BMD, width, dry weight, ash weight, total volume, minimum moment of inertia of cross-sectional areas, and polar moment of inertia of cross-sectional areas). As shown in Fig. 2A, BMD of the femur was significantly higher in the PK group, whereas BMD of the femur was not significantly higher in the MK group. In the MK group, femoral bone parameters (dry weight, ash weight, total volume and BMC) were significantly increased (Tables 1, 2 and 3). Femoral BMD was calculated per cm^3 (bone volume), so we considered the significant increase of bone volume as the reason why femoral BMD was not significantly higher in the MK group. Moreover, it will be also understood that the significant increase of bone volume was one of the reasons why femoral bone strength parameters (minimum moment of inertia of cross-sectional areas, and polar moment of inertia of cross-sectional areas) were significantly higher in the MK group. In addition, the increase of bone volume seemed to be caused by the increase of bone width not by the increase of bone length (Table 1). These results suggested that PK has the beneficial effects on increasing both of femoral BMC and BMD, while MK has the beneficial effects of increasing femoral BMC, bone volume, width and bone strength parameters. It is interesting that the effect of MK in the growth process on the width of the bone was suggested during bone remodeling.

Several *in vitro* studies demonstrated that both PK and MK-4 have beneficial effects on bone formation [25–27]. It was reported that MK-4 suppressed bone resorption [28–30], but PK did not have such an effect [31]. Hara et al. reported that the inhibitory effect of MK-4 on bone resorption may not be due to γ-carboxylation and that the side chain of MK-4 may play an important role in this inhibitory effect [31]. MK-4 significantly inhibited calcium release from mouse calvaria treated with $1\alpha,25(OH)_2D_3$ or prostaglandin E_2 (PGE_2), and the inhibitory effect of MK-4 on calcium release from calvaria was not affected by the addition of warfarin, an inhibitor of the vitamin K cycle while PK at the same doses did not have these effects [31]. Therefore, the inhibitory effect of MK-4 on bone resorption does not seem to be via γ-carboxylation.

A previous study demonstrated that MK-4 inhibited decreasing bone strength measured by employing a 3-point bending test induced by ovariectomy [15]. Bone quality has become an important issue in the prevention of osteoporosis [32], because the BMD is not the only factor that affects the occurrence of fractures [33,34]. The NIH consensus meeting proposed that bone strength is related to many factors including bone mineralization, architecture, turnover, and the concentration of organic proteins [35]. Recent studies have revealed that vitamin K functions as a ligand for nuclear steroid and xenobitoic receptor (SXR), as well as a cofactor for γ-carboxylase [36]. Inoue et al. identified novel SXR target bone-related genes regulated by MK-4 in osteoblastic cells using microarray analysis. Among extracellular matrix-related genes, they revealed that a small leucine-rich repeat proteoglycan, tsukushi, contributed to collagen accumulation [37].

Recently, we reported for the first time that both PK and MK-4 as nutritional factors enhance intestinal alkaline phosphatase (ALP) activity [38]. The high activity of intestinal ALP, which localizes at the brush border of the intestinal epithelium cells, suggests the participation of this enzyme in the transport of nutrients. In humans and rodents, a diet with a high fat content or the fat-feeding had elevated serum levels of intestinal ALP activity [39,40]. It was reported that intestinal ALP knockout mice showed no difference from the wild-type controls under the normal chow, however, when maintained long-term on a high-fat diet, the intestinal ALP knockout mice showed faster body weight gain

Table 3
Bone mineral measurements of femur.

	Total BMC (mg)		Cortical BMC (mg)		Cancellous BMC (mg)		Trabecular BMC (mg)	
Cont.	304.5 ± 7.2	*	248.1 ± 5.9		56.4 ± 1.6		48.1 ± 1.6	
PK	326.3 ± 5.9		265.6 ± 4.8		60.7 ± 3.1		53.6 ± 3.1	
MK	339.7 ± 7.9	##	272.7 ± 5.0	#	66.9 ± 3.1	#	58.7 ± 3.1	#

Each value represents mean ± S.E.
: Significant difference between the value of the control group and the PK group (: $p<0.05$).
#: Significant difference between the value of the control group and the MK group (#: $p<0.05$, ##: $p<0.01$).

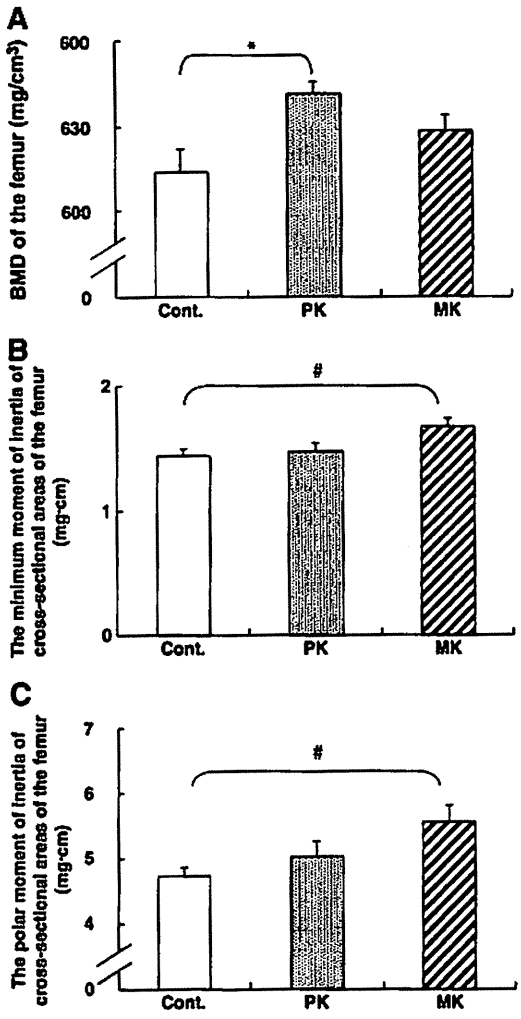

Fig. 2. Bone mineral density (BMD) and bone strength parameters of the femur in the control (Cont.), PK (PK), or MK (MK) diet group. Results are the mean ± S.E. of 7 or 8 animals. Significant difference between the PK and Cont. groups (*: $p<0.05$). Significant difference between the MK and Cont. groups (#: $p<0.05$). (A) BMD of the femur. (B) The minimum moment of inertia of cross-sectional areas of the femur. (C) The polar moment of inertia of cross-sectional areas of the femur.

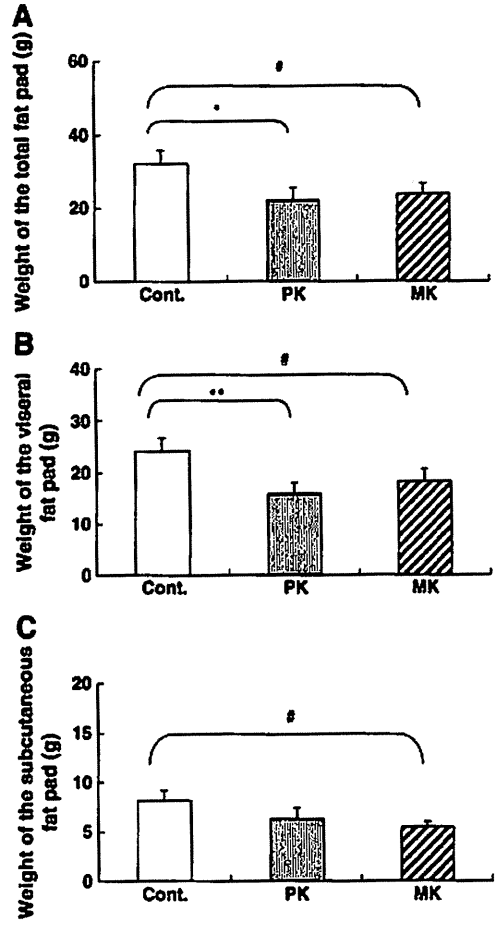

Fig. 3. Weight of the fat pad. (A) Weight of the total fat pad (g), (B) weight of the visceral fat pad (g), and (C) weight of the subcutaneous fat pad (g) after 82 days on the control (Cont.), PK (PK), or MK (MK) diet. Results are the mean ± S.E. of 7 or 8 animals. Significant difference between the PK and Cont. groups (*: $p<0.05$, **: $p<0.01$). Significant difference between the MK and Cont. groups (#: $p<0.05$).

compared with the wild-type animals [41]. These finding suggests the possibility that intestinal ALP may regulate not only phosphate metabolism but also fat metabolism.

In order to examine whether the effect of MK-4 on the bone volume was via GH secretion, we investigated the level of GH in serum [42–44]. Although the level of GH in the MK group tended to be higher than in the Cont. group, there was no significant difference, as shown in Table 5. In addition, we measured the levels of IGF-1 and IGFBP-3 in serum, which are markers of bone-related growth. As the results, IGF-1 and IGFBP-3 were similar among the three groups (Cont., PK, and MK) (Table 5), and the supplementation of MK-4 did not influence these growth factors affecting bone metabolism.

Interestingly, the addition of both PK and MK-4 to the Cont. diet may regulate not only bone strength but also fat deposition. Body weight gain (g/day), food intake (g/day) and food efficiency (body weight gain/food intake) were not significantly different among the three groups (Cont., PK, and MK). As shown in Fig. 3A and B, the weights of total and visceral fat in both the PK and MK groups were significantly lower than in the Cont. group. A previous *in vitro* study reported that MK-4 but not PK inhibited the formation of adipocytes in bone marrow cells [45]. It demonstrated that MK-4 inhibited the expression of osteoclast differentiation factor (ODF)/RANK ligand and the formation of osteoclast-like cells induced by $1\alpha,25(OH)_2D_3$, and that MK-4 specifically influenced the differentiation and functions of bone marrow cells. The present study revealed that both PK and MK-4 had effects on the reduction of fat deposition *in vivo*. Structural differences in the isoprenoid side chain may influence vitamin K metabolism, including the way it is transported, taken up by target tissues, and subsequently excreted. In the post-prandial state, PK is transported mainly by triglyceride-rich lipoproteins (TRL) and long-chain MKs mainly by low-density lipoproteins (LDL) [46]. As shown in Fig. 4B, the levels of triglycerides in both PK and MK groups were significantly decreased ($p<0.05$ and $p<0.001$, respectively). PK is converted into MK-4 and accumulates in extrahepatic tissues [47], and so we suggest that the regulation of fat deposition might be

Table 4
Biochemical parameters of serum.

Groups	Total protein (g/dl)	Calcium (mg/dl)	Phosphorus (mg/dl)	Alkaline phosphatase (U/l)	NTx (nmol/l)
Cont.	7.1 ± 0.1	10.6 ± 0.1	5.4 ± 0.6	118.7 ± 6.6	11.9 ± 0.5
PK	6.9 ± 0.1	10.4 ± 0.1	5.6 ± 0.5	136.1 ± 11.2	12.9 ± 0.8
MK	7.0 ± 0.2	10.5 ± 0.1	6.6 ± 0.4	125.6 ± 13.9	12.4 ± 0.9

Each value represents mean ± S.E.

Table 5
Hormone and cytokine parameters of serum.

Groups	GH (ng/ml)	IGF-1 (ng/ml)	IGFBP-3 (μg/ml)
Cont.	0.009 ± 0.001	1.92 ± 0.23	0.145 ± 0.007
PK	0.006 ± 0.002	1.69 ± 0.13	0.144 ± 0.003
MK	0.041 ± 0.017	1.43 ± 0.18	0.158 ± 0.006

Each value represents mean ± S.E.

mediated by not only dietary vitamin K, but also MK-4 converted from PK.

Some recent studies proposed that osteocalcin of undercarboxylated form is involved with a hormone in the endocrine regulation of energy homeostasis [48], and that picomolar amount of undercarboxylated osteocalcin regulates the expression of insulin genes and beta-cell proliferation markers whereas nanomolar amounts of osteocalcin affects adiponectin expression [49].

The effect of vitamin K on fat mass could be mediated through adiponectin regulation which itself has been found to be associated with fat mass. There is also another recent published work in humans that vitamin K supplementation with a daily dose of 0.5 mg of phylloquinone for 3 years had a protective effect on the progression of insulin resistance in older men [50]. These data indicate the need for further research and better understanding of the relationship among osteocalcin, its carboxylation, and vitamin K intakes.

The amount of vitamin K intake from the experiment diets is massive compared to nutritional requirements for vitamin K, and further dose–response studies are required to investigate whether long-term supplementation with doses in a more nutritional range would deliver the changes seen in this study.

Further studies on the effects of vitamin K on the regulation of the body composition would provide useful data on the prevention of lifestyle-related disorders, including osteoporosis.

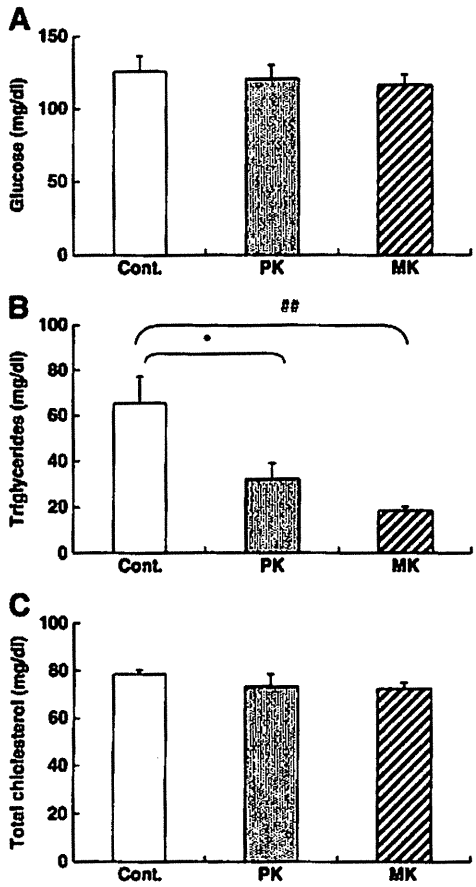

Fig. 4. Levels of serum glucose (A), serum triglycerides (B), and serum total cholesterol (C) after 85 days on the control (Cont.), PK (PK), or MK (MK) diet. Results are the mean ± S.E. of 7 or 8 animals. Significant difference between the PK and Cont. groups (*: $p<0.05$). Significant difference between the MK and Cont. groups (##: $p<0.01$).

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Spatiotemporal components of the 3-D gait analysis of community-dwelling middle-aged and elderly Japanese: Age- and sex-related differences

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Aim: To describe age- and sex-related differences in gait patterns of community-living men and women using 3-D gait analysis.

Methods: Subjects (n = 2006) aged 40–84 years participated in the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). Spatiotemporal components, including velocity, step length, step frequency, and double support time during a gait cycle, were calculated from 3-D coordinates and vertical force data. Velocity, step length and step frequency were normalized by leg length and acceleration due to gravity, and double support time was normalized to gait cycle duration.

Results: Spatiotemporal walking variables of brisk velocity and step length were significantly greater in men than in women, while comfortable velocity and comfortable and brisk step frequencies and double support times were greater in women than in men. Age-related changes were marked at 70–84 years in most spatiotemporal variables in both sexes during comfortable walking. During brisk walking, age-related changes were observed from a younger age than during comfortable walking, and there were sex-related differences.

Conclusion: The age-related gait alteration was obvious among those aged 70 years and older, and it accelerated markedly in women's brisk walking intensity. **Geriatr Gerontol Int 2011; 11: 39–49.**

Keywords: aging, gait, sex, velocity, walking.

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Author contributions: W. D. designed the study, obtained the funding, analyzed data and drafted the original article; R. K. interpreted data and advised on revising the article; K. H. Y. supervised data processing and prepared the article; and F. A. and H. S. originated the study, created the gait analysis program, supervised all aspects of its implementations, and contributed to obtaining the funding and revising the article. All authors conducted epidemiological studies on geriatric disease and human aging in Obu, Aichi, Japan, and read and approved the manuscript.

Introduction

Age-related impairment of ambulatory ability is a critical component for inhibiting activities of daily living (ADL). For instance, decreased gait velocity observed in elderly is an indicator of common distinct diseases[1,2] and falls,[3–6] which lead to functional dependence[7–11] or death.[12] The prevalence and incidence of gait disorders increase with age in elderly persons.[13,14] The early presence of dynamic postural stability may provide more essential information for preserving adequate mobility, delaying the onset of functional decline and encouraging early appropriate lifestyle changes to promote active healthy aging.[6,8,10,11,15]

Previous studies examined age-related changes in spatiotemporal gait parameters including velocity, step length, step frequency (cadence) and selected stride time variables (single and double support time and swing time).[7,8,10,16–21] These performance-based gait variables were often measured by a 3-D gait system that computes the motions of the body center of mass (COM) and each segment, which can accurately evaluate the control of dynamic balance during walking.[22,23] The COM velocity on the 3-D gait system identified the effect of age on older gait in limited comparison between young and older groups.[24–26] It showed that the 3-D analyses conducted have not determined from which age group the accelerated decline of gait started. The collection of data using a large sample size with a broad age range could resolve the issue.

Age-related gait studies have recruited either men or women, or both sexes have been analyzed together: a few studies previously focused on sex-related changes on gait pattern with advancing age. Callisaya *et al.*[8] revealed the effects of sex and age on gait velocity in elderly men and women aged 60–86 years. The results of other studies of various age ranges and groups[17,19,27] to determine which sex shows an earlier age of accelerated gait velocity decrease have differed. The conflicts may partly depend on the sampling and subject characteristics.

Therefore, to understand the aging process in gait measures across the adult lifespan, a large sample size ranging from young or middle-aged to elderly men and women should be warranted. We decided to reinvestigate the previous findings. In the present study, the gait of elderly subjects was investigated based on comfortable and brisk spatiotemporal gait parameters with a 3-D gait analysis system; a large number of subjects were recruited. We found the age-related changes in gait by sex among middle-aged and elderly men and women in Japan. This may contribute to a beneficial effect on assessing gait in elderly people and making an adequate walking exercise program suitable for targeted age groups.

Methods

Study sampling

The present gait analysis is part of the third phase of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA); this study includes medical, physiological, nutritional and psychological examinations. The study began in November 1997 (the first phase), and the third phase lasted from May 2002 to May 2004. The subjects were age- and sex-stratified random samples of the population, aged 40–84 years, who lived in Obu-shi and Higashiura-cho, Aichi, Japan. These participants were chosen from the residents registered with local governments. All subjects lived or had lived at their home in the community and had Japanese nationality.[28] The NILS-LSA was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology. Details of the NILS-LSA have been previously published.[28,29]

Of 2378 men and women aged 40–84 years in the third phase examination, 1017 men and 989 women (84.2% of all participants, Table 1) completed the walking tests and were included in the present analysis. The participants also completed a structured questionnaire dealing with their socioeconomic characteristics, cardiovascular risk factors and medical history.[28,29] Exclusion criteria included a current medical history of arthritis[6,8] and fractures (musculoskeletal disorders),[30] stroke[1] and Parkinson's disease (neurological disorders),[8,31] and ischemic heart disease and chronic bronchitis (Table 1).[32,33] These diseases were checked and excluded as the possible cause of gait disorders or spatiotemporal gait parameter changes by a physician before the walking tests. One participant who was diagnosed with dementia was excluded because she had a limited ability to comprehend or execute the test, which was judged by a physician. The existence of walking difficulty in activities of daily living (ADL)[11,15] was also excluded (Table 1). The participants who met the above-mentioned requirements and could walk 10 m independently without a walking aid were included in the current gait analysis and therefore 372 participants of the third phase examination were totally excluded.

Protocol

All participants wore short-sleeved T-shirts and shorts for testing. Shoes were made from the same material that had a vinylon/polyester and cotton blended upper part and a urethane foam outsole (Moonstar, Fukuoka, Japan), and were selected to exactly fit each participant's feet. Ten 2.5-cm diameter optical markers were placed on the participants' left and right sides on the fifth metatarsal heads, the lateral malleoli, the lateral epicondyles, and one-third of the way along the straight lines from the greater trochanters to the anterior

Table 1 Inclusion/exclusion characteristics of 2378 participants in the third wave examination of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), 2002–2004

Characteristics	Men	Women
Inclusion (n = 2006)		
Total (n (%))	1017 (50.7)	989 (49.3)
Age group (n (%))†		
40s	250 (12.5)	279 (13.9)
50s	302 (15.1)	265 (13.2)
60s	250 (12.5)	242 (12.1)
≥70	215 (10.7)	203 (10.1)
Exclusion (n = 372)		
Total (n (%))	187 (50.3)	185 (49.7)
Prevalence of disease (n (%))		
Stroke	42 (22.5)	23 (12.4)
Ischemic heart disease	41 (21.9)	41 (22.2)
Chronic bronchitis	7 (3.7)	3 (1.6)
Arthritis	26 (13.9)	56 (30.3)
Fracture	5 (2.7)	6 (3.2)
Dementia	–	1 (0.5)
Parkinson's disease	3 (1.6)	–
Walking difficulties in ADL (n (%))	50 (26.7)	54 (29.2)
Not completed walking test (n (%))	55 (29.4)	53 (28.6)

†χ^2-Test test examines significance among each age group and sex. Values are numbers (% of total at each inclusion/exclusion category) of samples. ADL, activities of daily living.

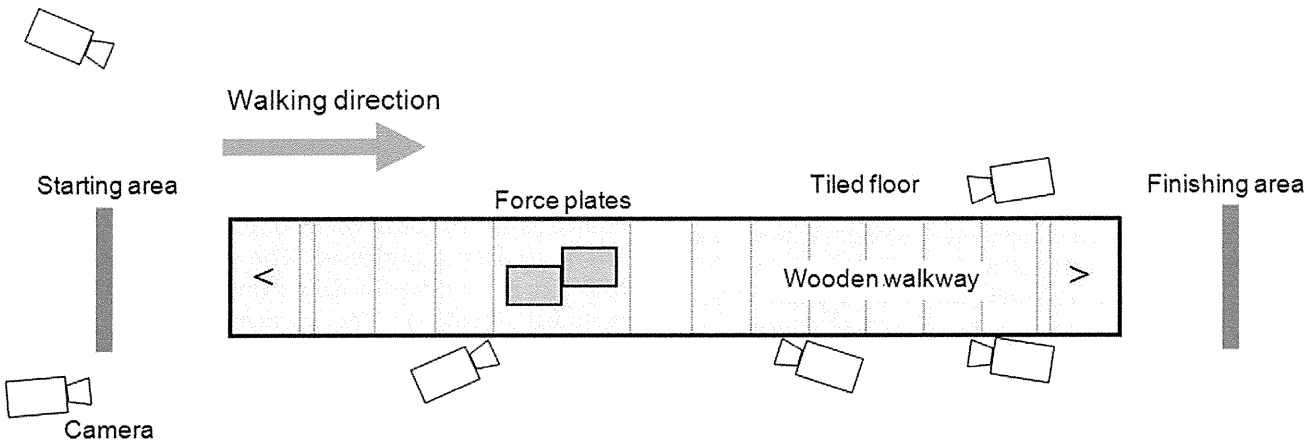

Figure 1 Setup of 3-D gait system: the 10-m walkway consisted of a wooden walkway. Six cameras were placed at various positions and two force platforms were embedded in the center of the walkway. Double support time in pre-swing phase of right foot was measured in this setting.

superior iliac spines and the acromions.[34] The subjects walked on a 10-m walkway at two speeds: (i) at a self-selected pace (comfortable walking); and (ii) as fast as possible without running (brisk walking). Each pace was repeated approximately twice on average. The walkway consisted of a tiled floor and a wooden walkway along the corridor (Fig. 1). The surface of the wooden walkway was covered with gray-colored, thin, stiff rubber, which measured 0.036 m in height from the tile floor surface of the corridor. Force platforms (0.6 m × 0.4 m) (9286; Kistler Instrumente AG, Winterthur, Switzerland), with surface colors similar to those of the walkways, were embedded in the center of the wooden walkway. The starting point for each trial was

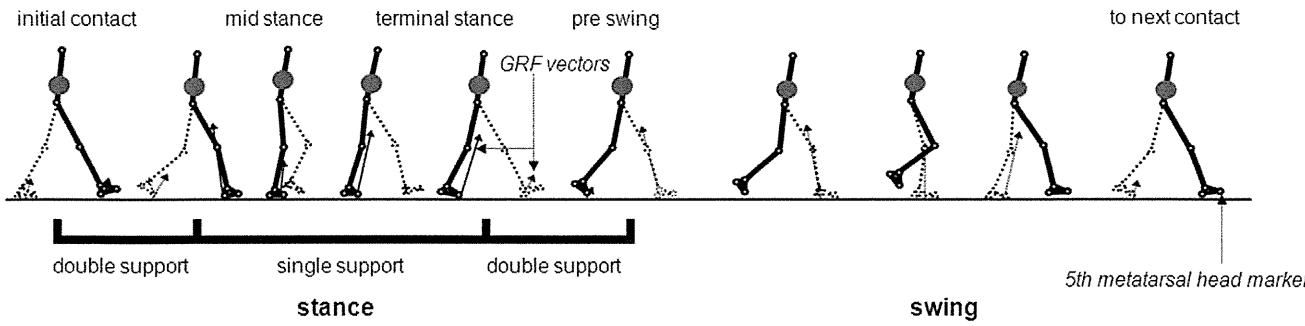

Figure 2 Definition of gait cycle using ground reaction force (GRF) and the fifth metatarsal head marker.

selected in relation to the foot contacts on the force platforms. The distance from each starting and departure point to the force platforms was approximately 3.5–4.5 m. One trial each of comfortable and brisk walking was used in the data analysis. The trials used were those that lacked the least data.

The Vicon 370 system (Oxford Metrics Ltd, Oxford, UK), which consisted of six cameras, was used to obtain the 3-D coordinates of the trunk, thighs, shins and feet. The calibration residual at each camera was set below 1.0 mm. The data were processed using a custom routine that was programmed by the Clinical Gait Analysis Forum of Japan.[34] The raw coordinate data at 60 Hz were digitally filtered with a fourth-order, zero-lag, Butterworth filter[22] with a cut-off at 5 Hz, and the raw ground reaction force data at 1200 Hz were digitally filtered with a cut-off at 10 Hz. The force data were interpolated to correspond with the coordinate data to synchronize the datasets. Smoothed coordinates of the lower extremities were used to construct a rigid link-segment model.[22] Segment masses and inertial properties were determined using previously reports[35] and the participants' mass and height, which were used for calculating COM.

Gait cycle and walking variable calculation

SAS ver. 9.1.3.[36] was used to automatically identify gait event times and each phase of the gait cycle based on kinematic and kinetic gait data. The divisions of the gait cycle are shown in Figure 2.[30] The gait event times for initial contacts and toe off were determined using vertical force data and the vertical motion of the optical marker on the fifth metatarsal head. The period from the first right initial contact to ipsilateral second initial contact was one gait cycle.[30]

Both the right and left leg motions were captured, and primarily the right stride was analyzed. Left leg motion was used for calculating the step length and double support times. The mean COM velocities, step lengths, step frequencies and double support times during a gait cycle were also automatically computed by SAS. The double support time was defined as the duration of time during which each foot was on the ground in the pre-swing phase. The mean COM velocity, step length, and step frequency were normalized as proposed by Hof[37] as follows:

Normalized COM velocity, $\hat{v} = \frac{v}{\sqrt{gl_0}}$,

Normalized step length, $\hat{l} = \frac{l}{l_0}$,

Normalized step frequency, $\hat{f} = \frac{f}{\sqrt{g/l_0}}$,

where v is actual mean COM velocity, l_0 is the leg length of each subject, l is the actual step length, f is the actual step frequency and g is the acceleration due to gravity (9.81 m/s^2). Leg length was measured from the ground to the greater trochanter during quiet standing. Patients with arthritis and fracture were excluded (Table 1), and no case of limited knee extension was observed in the present study. The double support time was also normalized by each subject's cycle duration, from right initial contact to next right initial contact (over one gait cycle).

For the calculation of walking variables, technical difficulties sometimes caused missing data due to the effect of occlusion while capturing motion. Thus, for example, the mean COM velocity over the gait cycle was calculated using data from 1716 men and women (85.5% of the total sample) during comfortable walking and using data from 1614 men and women during brisk walking (80.4%). To demonstrate the lack (or presence) of bias with respect to velocity data loss, the Student's t-test was used to compare the velocity between the group with all available data and that with data available only in the velocity category. The results showed that the velocities were not significantly different between the two groups, and this was confirmed for all walking variables.

Statistical analyses

All analyses were performed using SAS ver. 9.1.3. Sex differences were examined using the Student's t-test. For analysis of age differences, participants were divided

into eight groups based on sex and age (40–49, 50–59, 60–69 and 70–84 years for each sex). Trends in differences across all age groups in the walking variables were tested using the General Linear Model (GLM), and differences by age group were tested using the Tukey–Kramer method for each sex. $P < 0.05$ was considered statistically significant.

Results

The proportion of the sample drawn from each age group and each sex group was the same (χ^2-test, $P > 0.05$). The mean ± standard deviation age was 58.1 ± 11.4 years in men and 58.7 ± 11.4 years in women, which was not significant ($P > 0.05$).

The results of the GLM and Tukey–Kramer tests revealed age-related changes in each age and sex group. Descriptive statistics for all values are shown in Tables 2 and 3 and Figure 3. Mean COM velocities during comfortable and brisk walking significantly decreased with age in both sexes ($P < 0.001$). Age-related changes in the comfortable COM velocity were marked in the 70–84-year group compared with other age groups. Similar changes were found in the brisk COM velocity. The step lengths and frequencies followed these COM velocity patterns in both sexes during both comfortable and brisk walking.

These age-related changes occurred earlier in the middle-aged group. Earlier patterns involving brisk gait parameters were more apparent in women: for example, the brisk COM velocity decreased at 60–69 years in men and at 50–59 years in women, then the decrease accelerated at 70–84 years (Tables 2,3, Fig. 3). The step length and frequency followed these COM velocity patterns. The double support time during pre-swing was significantly increased with age only at the women's comfortable walking pace; it was significantly longer in the 70–84-year group compared to other age groups (Table 3, Fig. 3). The men's double support times showed no significant age-related differences among age groups (P for trend >0.05, Fig. 3).

Descriptive statistics and the results of sex differences for gait parameters are depicted in Table 4. The results of mean COM velocity differed according to walking pace: the comfortable COM velocity was significantly faster in women than in men ($P < 0.001$), and the brisk COM velocity was significantly faster in men than in women. Step length pattern was similar to COM velocity pattern: the brisk step length was longer in men than in women ($P < 0.001$), but the comfortable step length was not significantly different. On the other hand, women had a higher step frequency during both walking paces ($P < 0.001$). The results of the pre-swing double support time were equal to the step frequency.

Discussion

Mobility is essential for independence in the elderly. A better understanding of age-related changes in gait provides useful information for appropriate intervention programs targeting specific age groups.[8] The present cross-sectional, descriptive study showed spatiotemporal components of gait over one gait cycle among community-living middle-aged and elderly Japanese subjects. The sample of 1017 men and 989 women was large enough to allow analysis by age group,[17] and, to the best of our knowledge, the sample size is the largest to be published in which gait characteristics have been analyzed using a 3-D gait system. There was no disproportionate lack of gait data caused by difficulties in capturing the 3-D coordinates.

Mean COM velocities decreased with age, which is in almost complete agreement with previous results, despite the use of different measurement equipment and instrumentation.[16–21,25,29] The age-related decreases in the normalized COM velocities accelerated at 70 years and over were noted at a relatively later age compared with the previous reports: they showed the accelerated decline occurred in 50–59- and 60–69-year age groups,[17] at 62 years,[19] between 60- and 70-year age groups,[20] and at 65 years and in the 67–73-year age group.[18] The differences in age of accelerated decline among the previous and the present findings were likely due to the differences in method and data characteristics.

The brisk COM velocity decreases advancing with age were earlier compared with the comfortable walking. Some previous studies showed the age-related decrease was independent of walking pace,[18–20] while another reported that the decrease depended on the pace.[7] In a report by Bohannon on the comfortable and maximum walking speeds of adults aged 20–79 years,[7] walking speed was found to be influenced by the interaction of pace and age. This result matched our present findings that the age-related decrease was clearer during brisk walking than during comfortable walking. Moreover, these earlier age-related declines in the brisk COM velocities were apparent in women. Some studies reported that the critical age for marked velocity decrease did not differ by sex,[16,19] while another found the critical age to be earlier in men.[17] However, Callisaya *et al.*[8] showed women's walking velocity to be an earlier age-related change compared to men's parameters during the preferred speed of walking among the subjects aged 60 years and older. These results are in agreement with our own, though our data was particularly strong in the brisk parameters across middle-aged and elderly persons. The brisk walking task required greater forward momentum and increased demands in muscle activity[24,38–40] and aerobic capacity[33,41] might alter the spatiotemporal gait parameters accompanying aging.

Table 2 Men's normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking in each age group

Men: walking parameters by age group	Mean COM velocity				Step length				Step frequency				Double support times (pre-swing)			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Comfortable walking																
40s	211	0.524	0.053	0.517–0.531	240	0.892	0.065	0.884–0.900	207	0.587	0.043	0.582–0.593	208	14.8	1.5	14.6–15.0
50s	266	0.527	0.059	0.520–0.534	289	0.897	0.076	0.888–0.906	259	0.590	0.042	0.585–0.595	249	14.8	1.5	14.6–14.9
60s	218	0.523	0.067	0.514–0.532	240	0.901	0.089	0.890–0.913	215	0.583	0.046	0.577–0.589	205	14.5	1.6	14.3–14.7
70–	186	0.485	0.070	0.475–0.495	213	0.859	0.096	0.846–0.872	185	0.569	0.047	0.562–0.576	177	15.2	2.0	14.9–15.5
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s, 50s, 60s >70–				40s, 50s, 60s >70–				40s, 50s, 60s >70–				NA			
Brisk walking																
40s	190	0.705	0.078	0.694–0.716	229	0.998	0.074	0.989–1.008	180	0.707	0.070	0.696–0.717	173	13.3	6.0	12.4–14.2
50s	235	0.699	0.082	0.688–0.709	272	0.998	0.088	0.987–1.008	214	0.697	0.064	0.688–0.705	209	13.3	5.6	12.6–14.1
60s	191	0.678	0.079	0.667–0.690	237	1.000	0.094	0.988–1.012	185	0.685	0.066	0.676–0.695	180	13.4	5.0	12.6–14.1
70–	182	0.618	0.092	0.605–0.631	203	0.946	0.100	0.932–0.960	177	0.657	0.066	0.647–0.667	169	14.1	2.1	13.8–14.4
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s > 60s > 70–., 50s > 70–				40s, 50s, 60s >70–				40s > 60s > 70–., 50s > 70–				NA			

†Trend tests examine main effects of age in each gait parameter. ‡Tukey–Kramer tests examine the significant difference among each age group. '>' indicates the significant difference between the age groups, with *P*-value is less than 0.5. Values are numbers of samples (N), means (Mean), standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. Age group: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70–, 70–84 years age group. COM, center of mass; NS, not significant; NA, not applicable.

Table 3 Women's normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking in each age group

Women: walking parameters	Mean COM velocity				Step length				Step frequency				Double support times (pre-swing)			
by age group	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Comfortable walking																
40s	228	0.542	0.060	0.535–0.550	267	0.905	0.072	0.896–0.913	223	0.602	0.044	0.596–0.608	212	14.9	1.7	14.7–15.2
50s	224	0.547	0.066	0.538–0.556	252	0.902	0.082	0.891–0.912	219	0.607	0.051	0.600–0.614	214	14.9	1.7	14.7–15.1
60s	210	0.536	0.064	0.527–0.544	236	0.890	0.079	0.880–0.900	207	0.602	0.045	0.596–0.608	189	15.0	1.9	14.8–15.3
70–	173	0.472	0.071	0.461–0.483	189	0.833	0.093	0.820–0.847	169	0.570	0.051	0.562–0.578	148	15.8	1.9	15.5–16.1
P for trend†	<0.001				<0.001				<0.001				<0.001			
(Tukey–Kramer test)‡	40s, 50s, 60s >70–				40s, 50s, 60s >70–				40s, 50s, 60s >70–				70– > 60s, 50s, 40s			
Brisk walking																
40s	216	0.702	0.072	0.692–0.711	269	0.972	0.070	0.963–0.980	210	0.728	0.071	0.719–0.738	201	13.9	1.6	13.7–14.2
50s	215	0.675	0.080	0.665–0.686	252	0.960	0.087	0.950–0.971	212	0.706	0.073	0.696–0.715	209	14.2	1.7	13.9–14.4
60s	212	0.653	0.072	0.643–0.662	230	0.941	0.085	0.929–0.952	209	0.696	0.072	0.687–0.706	199	14.2	1.8	14.0–14.5
70–	173	0.577	0.084	0.565–0.590	187	0.890	0.109	0.875–0.906	163	0.651	0.064	0.562–0.578	157	14.3	8.8	12.9–15.7
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s > 50s > 60s > 70–				40s > 60s > 70–., 50s > 70–				40s > 50s, 60s > 70–				NA			

†Trend tests examine main effects of age in each gait parameter. ‡Tukey–Kramer tests examine the significant difference among each age group. '>' indicates the significant difference between the age groups, with $P < 0.05$. Values are numbers of samples (N), means, standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. Age group: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70–, 70–84 years age group. COM, center of mass; NS, not significant; NA, not applicable.

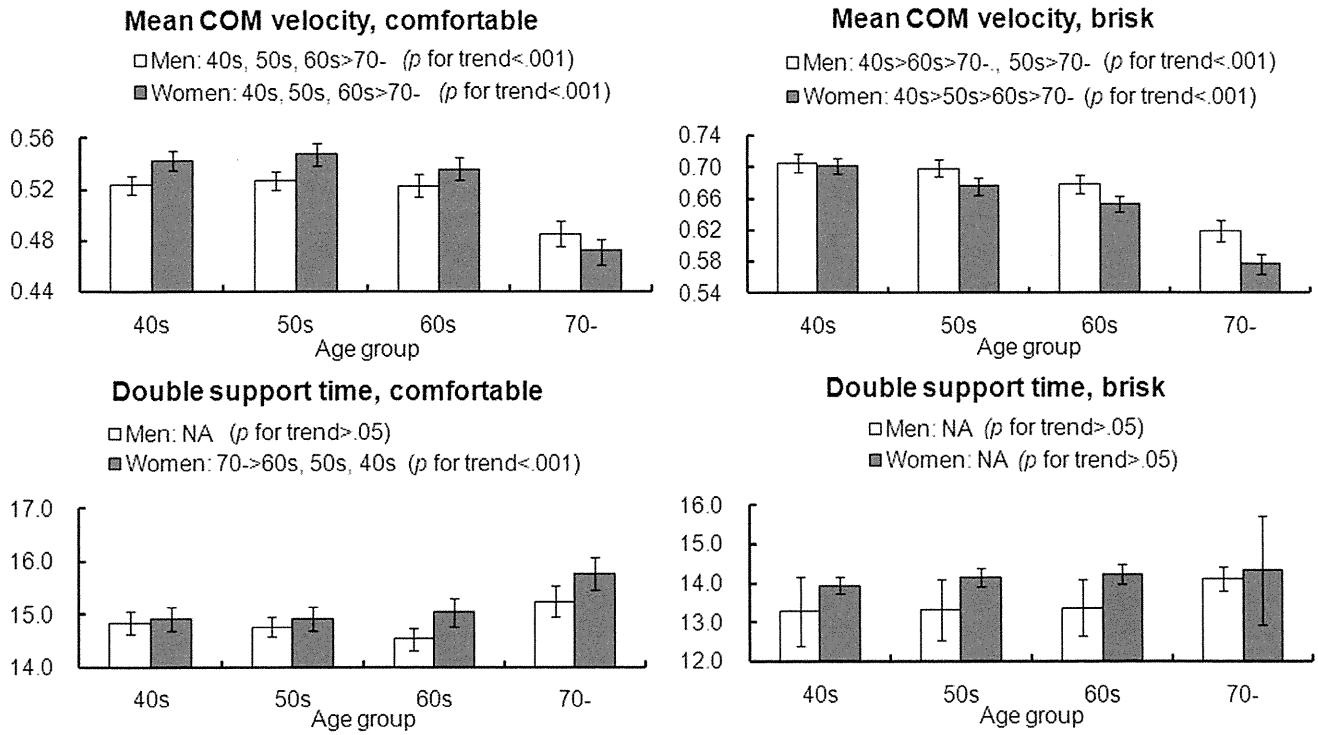

Figure 3 Age-related differences (trend tests and Tukey–Kramer tests); means and 95% confidence intervals of normalized mean center of mass (COM) velocities ($(m/sec)/\sqrt{((m/sec^2)\times m)}$) and double support times (s/s) during comfortable and brisk walking in men and women. Significant differences by age group in men and women are noted on the upper side of each figure. '>' indicates the significant difference between the age groups, with *P*-values of ≤0.05.

Table 4 Normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking among men and women

Walking parameters	Men				Women				*P*-value†
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	
Comfortable walking									
Mean COM velocity	881	0.516	0.064	0.512–0.521	835	0.527	0.071	0.523–0.532	<0.001
Step length	982	0.889	0.083	0.883–0.894	944	0.886	0.085	0.881–0.891	NS
Step frequency	866	0.583	0.069	0.580–0.586	818	0.597	0.045	0.593–0.600	<0.001
Double support time (pre-swing)	839	14.8	1.7	14.7–14.9	763	15.1	1.8	15.0–15.2	<0.001
Brisk walking									
Mean COM velocity	798	0.677	0.089	0.671–0.683	816	0.656	0.089	0.650–0.662	<0.001
Step length	941	0.987	0.092	0.981–0.993	938	0.945	0.092	0.939–0.951	<0.001
Step frequency	756	0.687	0.075	0.682–0.692	794	0.698	0.049	0.693–0.703	<0.001
Double support time (pre-swing)	731	13.5	5.0	13.2–13.9	766	14.2	4.3	13.9–14.5	<0.01

†Student *t*-tests examine the sex differences. Values are numbers of samples (N), means, standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. COM, center of mass; NS, not significant.

Further investigation should have discussed the difference between comfortable and brisk walking parameters.[38,42,43]

Age-related step length decreases during comfortable and brisk walking were almost concomitant with the COM velocity decreases, which was similar to the previous findings.[16,20] In brisk walking, however, age-related reduction in the step length seemed to be smaller than that in the step frequency compared with comfortable walking. For example, women's brisk step length decrease was 8.4% across middle-aged and elderly groups compared with their step frequency decrease of 10.7% (Table 3). This was observed also in men's. This may suggest that ambulatory ability observed in the COM velocity may be caused more by the step length during comfortable walking and the step frequency

during brisk walking in the elderly. This was also apparent in middle-aged women. The interpretation was limited qualitatively and should be further explored.

Step frequencies also decreased with age and this decrease was found even in middle-aged women during brisk walking. Previous studies in step frequency reported no age-related changes,[16,17,21] age-related decrease[8,18–20,25] and age-related increase.[26] Moreover, the current age- and sex-related decrease depending on required walking pace was not previously reported.[16,17] One explanation of these conflicts was that degree of the age-related reduction in step frequency was relatively less than that in other gait parameters such as velocity or step length.[8,17,19,20] Therefore, sample size, subject characteristics and measuring instruments may affect the age-related decrease in the step frequency.[16,25] Double support times in the present study did not increase with age, with the exception of women's comfortable data. On the other hand, exploratory analyses of actual values of double support times showed age-related increases in both sexes during both walking paces (data not shown, P for trend <0.001, <0.022). This shows that the double support as a percentage of one gait cycle remained almost constant in middle-aged and elderly subjects. Ferrandez *et al.*[32] found that double support time increased as velocity decreased, and that prolonged double support time was affected more by walking velocity than age.

The present study found brisk COM velocity and step length to be greater in men than in women. By contrast, step frequencies and double support times were greater in women than in men. This is characteristic of sex differences and is supported by previous findings.[8,17,21] Although the comfortable COM velocity was faster in women than in men, this is believed to be a result of the difference in body size as the actual comfortable COM velocity was significantly faster in men than in women (men, 1.46 ± 0.18 m/s; women, 1.43 ± 0.20 m/s; $P < 0.001$). The comfortable step length did not differ significantly between either sex group, perhaps because of the slower men's COM velocity.

The present gait data may give some insight into gait assessment and preventive walking exercise programs for older persons as previously reported.[42,44,45] The values for the gait parameters during one gait cycle may be useful to clinicians judging the ambulatory ability of patients from a short indoor walk.[7,42] Patients whose gait parameters are lower than that of their appropriate age group are at increased risk of ADL difficulties.[8,11] Comfortable and brisk walking velocities are predictive of adverse outcomes such as loss of physical function, requirement of caregivers, hospitalization and increased mortality in elderly persons.[8,10–12] Decreased step length and prolonged double support time are correlated with fear of falling and/or future fall risk.[4,5,9] Also, the other gait parameters such as gait velocity,[9,11] stride-to-stride variability[4] and lateral sway[3,5,6,46] are associated with the falling events. We did not directly ascertain whether the participants had a history of falls and/or a fear of falling in our gait parameters. Further work should confirm which gait measure is the best independent predictor for future fall risk in a large sample.

A moderate workload prescription in walking exercise programs should be given by controlling both step length and step frequency during comfortable walking in the elderly. Brisk walking, which is recommended for moderately vigorous endurance training and has a high impact compared to comfortable pace walking, might be considered for middle-aged women and the elderly to improve physical functions such as muscle strength[7,40,43] and/or cardiovascular fitness.[33,41]

This study has some limitations. Some previous gait investigations used the results of several trials or mean values of gait, while we used gait data from one trial of each participant. This was done because of technical difficulties in the automatically computed 3-D gait parameters. Next, the conjunction of our excluding criteria with the potential diseases might overestimate gait disorders: the elderly subjects were more likely to be healthy and physically fit. Moreover, patients with dementia were considered to be less in the present sample. The general comparability of the present gait variables with previously reported data is limited because of the lack of data for young adults in their 20s and 30s. Furthermore, our cross-sectional analysis approach could not demonstrate a cause-and-effect relationship from aging. We are planning longitudinal studies to further determine the effects of aging on gait. The present study included regional limitations such as race, culture, lifestyle, genetics and socioeconomic status which also may be important. However, the findings did permit age- and sex-related differences in gait to be clarified in the elderly.

In conclusion, age- and sex-related gait alterations were apparent in one gait cycle of walking in a large sample of community-dwelling, middle-aged and elderly Japanese men and women, when analyzed by a 3-D gait system. There were marked age-related gait differences in subjects aged 70 years and over compared to subjects aged 40–69 years during comfortable walking, and subtle differences were also observed in subjects aged 40–69 years during brisk walking. The earlier age-related changes were clearer in women than in men. These results may guide the assessment of gait patterns attributed to usual aging and to develop moderate exercise programs for the elderly.

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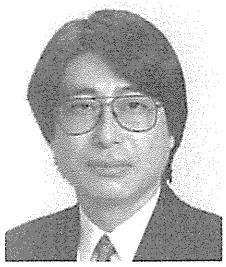
運動器疾患の長期縦断疫学研究

Longitudinal epidemiological study on locomotive organ disease



下方浩史(写真)　安藤富士子
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国立長寿医療研究センター予防開発部[1]，愛知淑徳大学健康医療科学部[2]

◎運動器症候群の予防方法を解明するためには，その危険因子を明らかにすることが必要である．一般住民を対象とした長期縦断疫学研究により，運動器疾患罹患の実態を明らかにするとともに，栄養や運動，疾病罹患，飲酒や喫煙などの生活習慣，遺伝的素因などと加齢にかかわる運動器疾患の発症との関連を解明することができる．国立長寿医療研究センターでは無作為抽出された一般地域住民を対象に，老化・老年病に関する基礎データの収集のための長期にわたる集団の大規模な縦断研究「老化に関する長期縦断疫学研究(NILS-LSA)」を平成9年度(1997)より行っている．NILS-LSAでの調査から，日本人全体で骨粗鬆症は1,000万人，変形性膝関節症は3,000万人を超える患者がいると推計された．現在，遺伝子や生活習慣，体力，栄養などさまざまな要因についての縦断的な解析から高齢者の運動器疾患のリスク要因を明らかにし，予防方法を開発するための研究を行っている．

Key word：長期縦断疫学，老化，骨粗鬆症，変形性関節症

運動器症候群(ロコモティブシンドローム)とは，運動器の障害により要介護になるリスクの高い状態になることである．実際に要介護となる要因として関節疾患，転倒・骨折が大きな割合を占めている．高齢者における関節疾患のほとんどは変形性関節症であり，また高齢者の骨折は骨粗鬆症がおもな要因となっている．変形性関節症と骨粗鬆症に限っても，運動器症候群の推計患者数は4,700万人(男性2,100万人，女性2,600万人)に達するという[1]．日本社会の高齢化に伴って，今後さらに急速にこれらの患者数は増大していくものと推定されている．また，運動器症候群は認知症の要因となるとも考えられており，運動器症候群の予防に関する研究は，日本において今後の進展が強く望まれる分野である[2]．

運動器症候群の予防方法を解明するためには，その危険因子を明らかにすることが必要である．無作為抽出された一般住民を対象とした長期にわたる観察研究は，一般住民の間での運動器疾患罹患の実態を明らかにするとともに，栄養や運動，疾病罹患，飲酒や喫煙などの生活習慣，遺伝的素因などと加齢にかかわる運動器疾患の発症との関連を解明するために不可欠である．こうした研究により，どのような素因をもち生活を送っている人が，どのような確率で運動器疾患に罹患していくのか，どのように対策を取れば，どのくらいの確率で予防できるのかを明らかにすることができる[2]．

長期縦断疫学研究

国立長寿医療研究センターでは老化・老年病に関する基礎データの収集のために長期にわたる集団の大規模な縦断研究「老化に関する長期縦断疫学研究(NILS-LSA)」を平成9年度(1997)より行っている(図1)[3-7]．対象は地域住民から年齢・性別に層化し無作為抽出された，観察開始年齢が40～79歳の男女である．抽出によって選定された人を説明会に招いて，検査の目的や方法などを十分に説明し，インフォームドコンセントを得たうえで検査を実施している．追跡中のドロップアウ

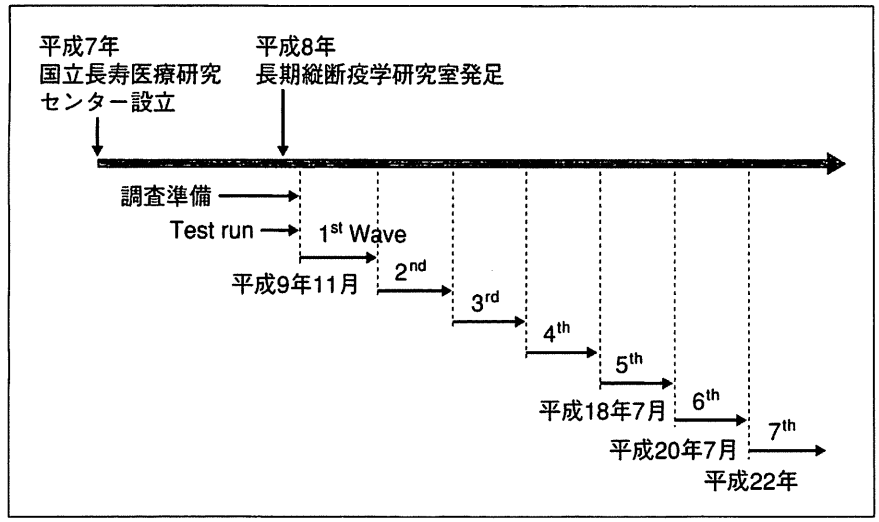

図 1　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の経緯
NILS-LSA では地域在住の中高年者約 2,400 人の 10 年以上にわたるデータが蓄積されている.

トは，同じ人数のあらたな補充を行い，定常状態として約 2,400 人のダイナミックコホートをめざしている.

施設内に設けられた専用の検査センターで朝 9 時から夕方 4 時までの間に分刻みでスケジュールを組んで，1 日 7 名，週 4 日，年間を通して詳細な老化に関連する検査を行っている．平成 12 年(2000)4 月に 2,267 名の基礎集団が完成し，以後は 2 年ごとに検査を繰り返し行っており，現在は第 7 次調査を行っている．調査項目は頭部 MRI や超音波断層，骨密度測定，腹部 CT など最新の機器を利用した医学検査のみならず，詳細な生活調査，栄養調査，運動機能調査，心理検査など広汎で精度の高い内容である(図 2)．運動器疾患に関連した検査としては，DXA 法による全身骨，腰椎，左右大腿骨頸部の 4 スキャンでの骨密度測定，末梢骨定量 CT 検査法(pQCT)による橈骨 16 スキャン，左右膝 X 線撮影，胸椎腰椎 X 線撮影，膝関節機能検査，転倒調査，膝痛調査，腰痛調査，骨折調査，骨代謝マーカー検査などを実施している．調査開始当初より，調査参加者のほぼ全員からの血液サンプルを用いて DNA を蓄積している．これほど背景因子が詳細に検討されている一般住民の DNA 試料の蓄積は，国内外でもほかにはほとんどないと思われる[8,9].

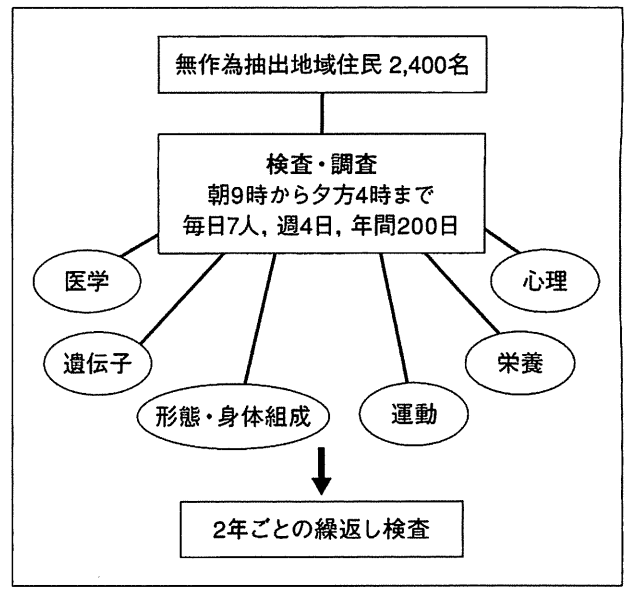

図 2　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の概要

加齢に伴う運動器疾患罹患の実態

NILS-LSA の第 5 次調査に参加した 40～88 歳の男性 1,200 名，女性 1,219 名の合計 2,419 名を対象として，立位で両膝の X 線写真を撮影し，Kellgren-Lawrence 分類(KL 分類)[10]にて変形性膝関節症を grade 0 から gradeⅣまでに分類し，gradeⅡ以上を変形性膝関節症と診断した．また，gradeⅢ以上を膝関節高度変形として，10 歳ごとの年齢別および性別に有病率を算定した．図 3 に示すように，変形性膝関節症は男性よりも女性に多く，年

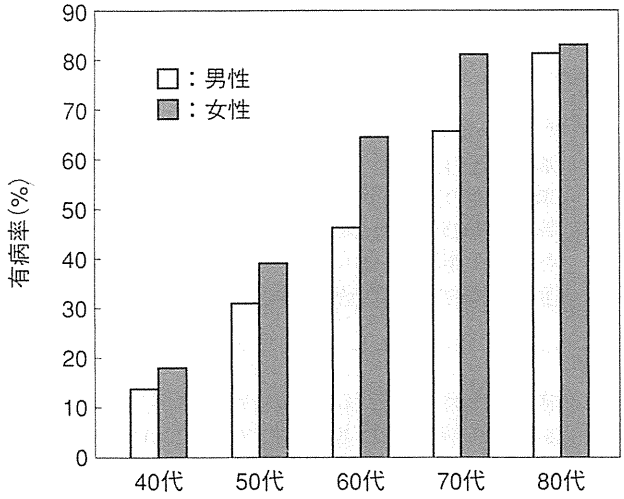

図 3　年代別，性別の膝変形性関節症の有病率
(Kellgren-Lawrence 分類 grade Ⅱ以上)

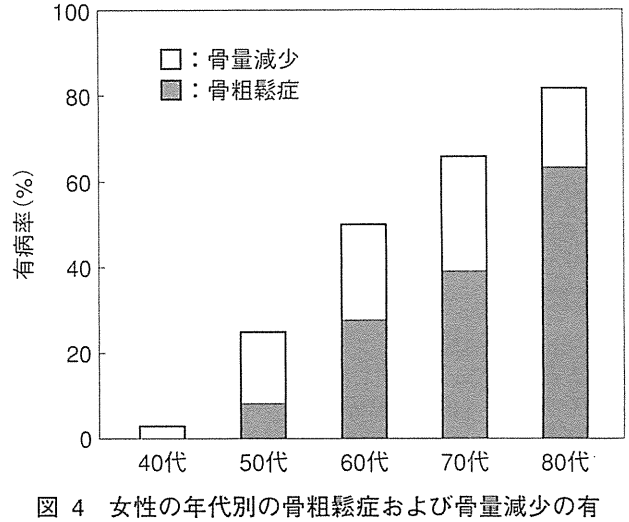

図 4　女性の年代別の骨粗鬆症および骨量減少の有病率(日本骨代謝学会診断基準による腰椎骨密度からの判定)

齢とともに有病率は上昇する．40 歳以上の女性全体での有病率は 52.3%，男性で 43.5%であった．また，KL 分類 grade Ⅲ以上の膝高度変形保有率は女性のほうが男性よりも 2 倍以上多く，また女性では年齢とともにその率は大きく上昇していた．上記の有病率を用いて日本人全体の人口構成から有病率を計算すると，男性 1,278 万人，女性 1,950 万人の合計 3,228 万人と推定された．

日本骨代謝学会の診断基準[11]を用いて，DXA 法で計測した腰椎骨密度(第 2, 3, 4 腰椎の平均骨密度)および右大腿骨頸部骨密度により，性別，年齢別に骨粗鬆症の有病率を算定した(図 4)．50 歳以上の女性の有病率は，腰椎 BMD の判定の場合 26.1%，大腿骨頸部 BMD 判定の場合 21.3%であった．骨粗鬆症・骨量減少の年代別有病率は，どちらの部位の判定でも加齢で高くなり，とくに 60 歳代で急に高くなった．腰椎に比べ，大腿骨頸部判定の場合，50, 60 歳代での有病率は低かった．50 歳以上の男性の骨粗鬆症有病率は，腰椎 BMD の判定の場合 7.6%，大腿骨頸部 BMD 判定の場合 10.3%であった．骨粗鬆症・骨量減少の年代別有病率は，大腿骨頸部の判定において 60 歳代以降，男性でも加齢で高くなっていた．この結果をもとに，今回得られた骨粗鬆症有病率から見積もられる骨粗鬆症患者数は，腰椎骨密度による有病率を用いると 50 歳以上の女性で約 811 万人，50 歳以上の男性で 189 万人と推計され，大腿骨頸部では女性 685 万人，男性 250 万人となる．男女合計で骨粗鬆症患者数は 900 万～1,000 万人と推定された．

骨粗鬆症疾患ゲノム研究

骨粗鬆症は生活習慣病であり，カルシウム摂取の不足ややせ，運動不足などの危険因子が指摘されている[2]．一方で，骨粗鬆症の危険因子として家族歴がある．他の多くの生活習慣病や老年病と同じように，骨粗鬆症は遺伝的素因と生活習慣や加齢などが複雑に影響しあって発症する多因子疾患であると考えられている．疾患によって遺伝的要因の影響の強さは異なる．人種差や環境，生活習慣による違いはあろうが，アメリカの Framingham スタディの報告では，骨密度の遺伝率(heritability)は約 60%と推定されており，遺伝的な要因は比較的大きいと思われる[12]．NILS-LSA では，これまでに骨密度と有意な関連のあった 31 種類の遺伝子多型についてあらたに発見，あるいは確認の報告を行っている(表 1)[7]．

骨粗鬆症や骨密度への遺伝子多型の影響は，直接的な影響よりもむしろ生活習慣や環境因子による骨への影響を遺伝子多型が修飾する部分が大きい可能性がある．図 5 は著者らの調査の解析結果である．閉経女性の DXA 法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ERα)遺伝子 *Xba* Ⅰ多型の影響について検討した[13]．除脂肪体重として求めた筋量が多ければ骨密度は高いが，その影響は AA 型よりも AG/GG 型のほうが

表 1　NILS-LSAにおいて骨密度との関連をあらたに発見または確認した遺伝子多型

略号	遺伝子多型	骨密度への影響
カルシウム向性ホルモンおよび受容体		
VDR	vitamin D receptor(A-3731G)	男性の CC 型で大腿骨頸部の骨密度が高い
ESR1	estrogen receptor α(PP/pp)	高齢女性の CC 型で骨密度が低い
ESR1	estrogen receptor α(XX/xx)	高齢女性の GG 型で骨密度が低い
OST	osteocalcin(C298T)	閉経女性の TT 型で骨密度が低い
ADR	androgen receptor(CAG repeat)	未閉経女性の CAG リピートが多いと骨密度が低い
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1(T-34C)	閉経女性の CC 型で骨密度が低い
サイトカイン，成長ホルモンおよび受容体		
IL-6	interleukin-6(C-634G)	閉経女性の GG 型で橈骨遠位の骨密度が低い
TGF-β	transforming growth factor-β1(T29C)	高齢女性の TT/TC 型で橈骨の骨密度が低い
OPG	osteoprotegerin(T950C)	未閉経女性の CC 型で橈骨近位の骨密度が低い
OPG	osteoprotegerin(T245G)	閉経女性の GG 型で大腿骨頸部骨密度が低い
CCR	chemokine receptor 2(G190A)	若年男性と閉経女性の GG/GA で骨密度が低い
骨基質関連蛋白		
MMP1	matrix metalloproteinase-1(1G/2G at-1607)	閉経女性の GG/GG 型で橈骨遠位骨密度が低い
MMP9	matrix metalloproteinase-9(C-1562T)	男性の CT/TT 型で骨密度が低い
COL	collagen type 1(G-1997T)	閉経女性の GG 型で骨密度が低い
ICAM-1	intercellular adhesion molecule-1(Lys469Glu)	閉経女性の AA 型で骨密度が低い
PLOD1	procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	未閉経・閉経女性の GA/AA 型で骨密度が低い
CX37	connexin 37(Pro319Ser)	男性の TT 型で骨密度が低い
その他		
KLOT	klotho(G-395A)	閉経・未閉経女性の GG 型で骨密度が低い
MTP	microsomal triglyceride transfer protein(G-493T)	未閉経女性の TT 型で骨密度が高い
VLDLR	VLDL receptor(triplet repeat)	男性の CGG リピート 8 以上で骨密度が高い
ALAP	adipocyte-derived leucine aminopeptidase(Lys528Arg)	未閉経女性の GA/AA 型で骨密度が低い
LIPC	hepatic lipase(C-514T)	閉経女性の TT 型で骨密度が低い
CNR2	cannabinoid receptor 2 gene(A/G, rs2501431)	未閉経・閉経女性の AA/AG 型で骨密度が低い
PON1	paraoxonase-1(Gln192Arg)	閉経女性の GG 型で骨密度が低い
PON1	paraoxonase-1(Met55Leu)	閉経女性の TT 型で骨密度が低い
PON2	paraoxonase-2(Cys311Ser)	閉経女性の CC 型で骨密度が低い
DRD4	dopamine D4 receptor(C-521T)	男性の CC 型で骨密度が低い
FOXC2	forkhead box C2(C-512T)	男女ともに T アリルで骨密度が低い
PLN	perilipin(C1243T)	男性の C アリルで骨密度が低い
MAOA	monoamine oxidase A(uVNTR)	未閉経・閉経女性のリピート 4 未満で骨密度低い
SH2B1	Src-homology-2-B(Ala484Thr)	未閉経・閉経女性の A アリルで骨密度が低い

強い．AG/GG 型の多型をもつ人は筋量を増やすことが，AA 型の人よりも骨粗鬆症の予防には効果的であることがわかる．筋量が少ない集団では AA 型のほうが骨密度は高いが，筋量が多い集団では AG/GG 型のほうが骨密度は高いという逆転が生じており，このため対象集団の筋量が異なれば，遺伝子多型の骨密度との関係はまったく逆になってしまう．遺伝子以外の個体差が十分に検討されていないことが，ゲノム研究での再現性が乏しいことの要因のひとつになっている可能性がある．

感受性遺伝子多型をもっていても発症しない人もいる．その要因を探るというアプローチもある．感受性遺伝子多型をもっていて発症した人，発症していない人について生活習慣などの要因を詳細に比較検討することで，感受性遺伝子をもっていても骨粗鬆症をどうすれば予防できるかを明らかにすることができる．さらに生活習慣などの修飾可能な危険要因については，その縦断的変化についての検討も必要である．特定の遺伝子多型をもつ人が，たとえば身体活動量を 2 倍にしたとき骨密度はどう変化するのか，遺伝子多型によってその効果にどのような差があるのかを明らかにする

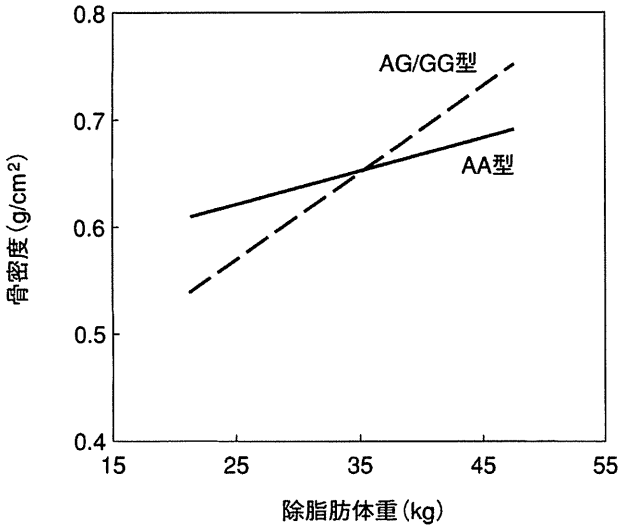

図 5　閉経女性のDXA法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ERα)遺伝子 *Xba I* 多型の影響[13]

除脂肪体重，すなわち筋量が多ければ骨密度は高いが，その影響はAA型よりもAG/GG型のほうが強い．

ことが，遺伝子多型を利用した実際の予防指導の際には重要である．こうしたデータを蓄積するためには，多数の集団で長期にわたった詳細な生活習慣や環境要因の調査が必要である(「サイドメモ」参照)．

運動器疾患のリスク予想と予防

骨代謝マーカー測定によって骨粗鬆症や骨量減少の予測ができるかをNILS-LSAで検討した．骨代謝マーカーとしてオステオカルシン(OC)，骨型アルカリホスファターゼ(BAP)，尿中Ⅰ型コラーゲン架橋N-ペプチド(NTx)，デオキシピリジノリン(DPD)を測定したところ，女性の腰椎でOC，BAP，NTxが，女性の大腿骨頸部でDPD，BAP，NTxが，男性の大腿骨頸部でBAPが6年後の骨粗鬆症や骨量減少の発症に有意に関連しており，これらのマーカーから将来の骨粗鬆症や骨量減少の発症を予測できる可能性が示された[14]．

NILS-LSAでは，生活習慣や環境要因との相互関係を考慮した骨粗鬆症の遺伝要因の検討も順次進めている．DXA法による骨粗鬆症診断結果と，握力，脚筋力など運動・体力に関する要因，カルシウム，ビタミンDなど栄養に関する要因，BMI，除脂肪体重など体格・体型に関する要因，そのほか嗜好，閉経，骨代謝マーカーを含む血液尿検査結果などの項目の追跡による縦断的なデータについて網羅的に検討を行うことで，それぞれ骨粗鬆症と関連の強い要因を抽出する．抽出された要因と遺伝子多型との相互作用を網羅的に検討し，その結果から最終的に骨粗鬆症と関連する生活習慣要因，遺伝子多型，生活習慣要因と遺伝子多型の交互作用を抽出し，骨粗鬆症の予測を行う総合的なシステムの構築を行っている．長期縦断研究によりこうしたシステムが完成すれば，骨粗鬆症の医療や予防の実用化へ一歩前進するものと期待される．

おわりに

高齢化が急速に進む日本の社会において，高齢者の健康維持・増進はきわめて重要な課題である．高齢者が健康に長生きできることは国民の共通の願いであり，これを実現することが急務である．高齢者の運動器疾患は直接の死因とはならない場合がほとんどではあるが，高齢者のQOLを阻害し，寝たきりや廃用症候群を引き起こし，認知症や肺炎の要因ともなる．高齢者の運動器疾患の予防と治療は高齢者の健康長寿を考える場合には欠かすことができない．そのためのエビデンスを集積する研究として，疾患そのものだけでなく，

サイドメモ　縦断研究

加齢による変化を検討する方法には大きく分けて，横断的方法と縦断的方法の2つがある．縦断的研究は同一の個人を継続して観察し，加齢による実際の心身の変化，加齢に関連する要因，発育，発達，老化，寿命などをとらえようとするものである[1-4]．一方，さまざまな年齢を含む集団を設定して種々の検査を一度に実施し，1歳ごとの，あるいは5歳，10歳ごとの年齢群で検査値がどのように異なるのかを検討し，その差を加齢変化とする方法が横断的研究である．一度の調査で終了してしまう横断研究に比べて経時的な追跡を行う縦断研究は，結論が出るまでに一般に数年から10年以上もの期間を要し，調査を継続するための費用や人材の確保も必要である．しかし，加齢変化の観察を行うためには横断的観察のみでは加齢による変化を正確にとらえることができない．