Table 1 Inclusion and exclusion criteria

Inclusion criteria
Postmenopausal osteoporosis[a]
Over 70 years old
Ambulatory patients who do not require any help
Able to answer QOL questionnaire
Corresponds to more than one of A-TOP's risk factors for fracture[b]
Exclusion criteria
Metabolic bone diseases other than osteoporosis[c]
Contraindication to the drugs (ALN or alfacalcidol)
Dysfunction in communication of intentions
Severe degenerative deformation of vertebra
Abnormal heart function
Abnormal hepatic function
Abnormal kidney function
Treatment of osteoporosis by bisphosphonate within 6 months prior to the present study

These thresholds were decided by risk analysis by the A-TOP research group

[a] Over 1 year after menopause

[b] Pre-existing vertebral fracture number ≥ 1; BMD $\leq$ Young Adult Mean -3 SD; Urinary DPD ≥ 7.6 nmol/mmol Cr; or NTX $\geq$ 54.3 nmol BCE/mmol Cr

[c] Hyperparathyroidism and hyperthyroidism were excluded

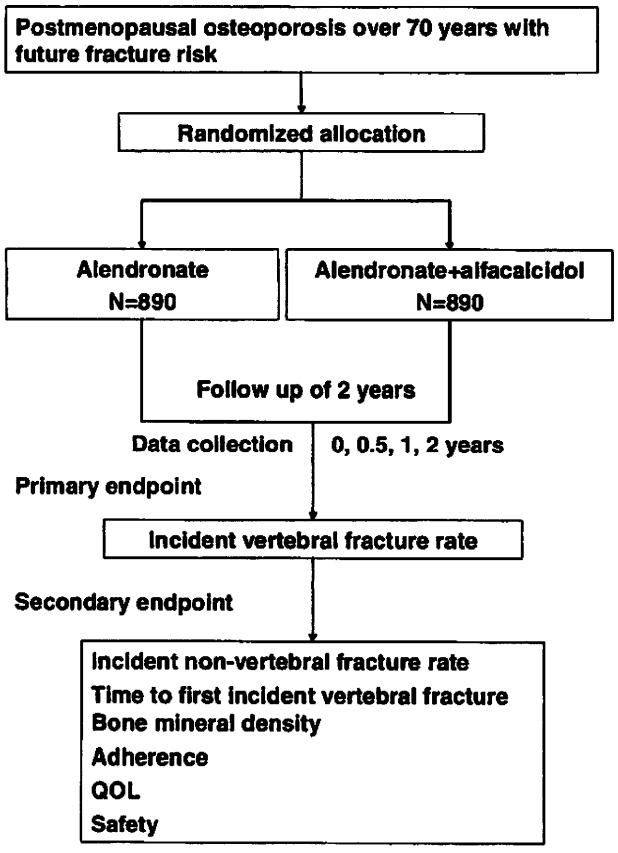

Fig. 1 Study design and outcomes

participants were selected by the practitioners and registered by Japan Clinical Research Support Unit (JCRSU), and then randomly allocated with a modified minimization method using age, number of pre-existing vertebral fracture number, bone mineral density (BMD) and value of bone metabolic marker into the group to be administered only ALN or the group that was to be administered both ALN and alfacalcidol. Registration and allocation of the participants were carried out on the Internet. After initiation of the assigned treatment, clinical data were collected at intervals of half a year for 2 years by I'cros Co., Ltd., through their visiting data collection service. Data were input to the database using a web system developed by ING Corporation. The primary endpoint was to compare the incident vertebral fracture rate between the intervention arms. The secondary endpoints were to compare the differences in the time to first incident vertebral fracture, non-vertebral fracture rate, bone mineral density, adherence, QOL and safety (Fig. 1). In addition, sub-group analyses categorized by baseline characteristics such as age, body mass index (BMI), serum 25-hydroxyl vitamin D levels, the number of pre-existing vertebral fractures and fracture grade were candidate factors. If participants wanted to change the designated treatment because of side effects or occurrence of fractures, they were permitted to do so, and follow-up observations were continued. Please see Table 1 and Fig. 1.

Sample size

Assumptions regarding the fracture rate in the ALN group were made based on a paper by Kushida et al. (Phase III trial for alendronate), in which it is reported that there was a 12.2% fracture rate during observations conducted over 2 years [8]. Since there are not much data on concurrent use of ALN and alfacalcidol [18], the authors' expectations were such that the effects of ALN would be added to those of alfacalcidol and that the hazard ratio of the alfacalcidol combined arm to ALN alone would be 0.64 [19]. The sample size was then estimated to be 890 cases per arm (two-sided alpha = 0.05, power = 0.8), taking account of a dropout rate of 10% referring to the value of the prior clinical trial of fracture intervention [4].

Fracture evaluation

X-ray films of conventional lateral radiographs of lumbar and thoracic vertebrae were taken and collected by I'cros Co., Ltd. After masking the patient's information, two

independent readers (orthopedist, TN and radiologist, MF) simultaneously reviewed films from T4 to L4 in chronological sequence and graded vertebral fracture based on a semi-quantitative method [20]. Before the start of the study, these two observers held meetings to make adjustments between their own criteria for grading vertebral fractures. When the diagnosis of pre-existing fractures made by the reviewers differed from those made by the practitioners, the reviewers' diagnosis was adopted preferentially. If inconsistencies arose between the readers in diagnosing pre-existing and incident vertebral fractures, the two readers negotiated between themselves to reach a consensus. Incident bone fractures other than those of the vertebrae were comprehended from the chart, and the occurrence of fractures was confirmed based on X-ray films or a record of the operation.

Clinical data

BMD at the lumbar vertebrae, hip (proximal femur), distal radius (dual energy X-ray absorptiometry) or left-sided second metacalpal bone (microdensitometry) was measured at baseline and at 6-month intervals for 2 years at each institute. The data of BMD obtained from the different machines and from different bone sites were calculated as the percentage change in each time point from the baseline value. The statistical difference in change of BMD between the group that received combined treatment and the group that was administered only ALN was compared based on each set of data for BMD for the different bone sites. Body height was measured at baseline, 12 and 24 months. Bone turnover markers (urinary type I collagen cross-linked N-telopeptide or urinary excretion of deoxypyridinoline) were measured at baseline and again 6 months after initiating treatment. QOL was assessed by using self-administered questionnaires (JOQOL and EQ-5D) at baseline and at 6, 12 and 24 months after initiating treatment [21]. Serum samples were sent to the central laboratory (SRL Co., Japan), and 25-hydroxyl vitamin D concentrations were measured. Other routine biochemical examinations were carried out at baseline and at 2 years after initiating treatment in order to estimate biochemical adverse events. All adverse events were reported to JCRSU, coded by MedDRA, and categorized as either "known" or "unknown." If an unknown adverse effect occurred, it was reported to the investigator and ethical committee.

Ethics and registration

Ethical issues regarding protocol were reviewed by the ethical committee for JOINT under the Declaration of Helsinki (Dr. Rikushi Morita, Chairman). If it turned out that a patient was at a disadvantage under observation, the ethical committee was given permission to stop the protocol. This study was registered at UMIN-CTR (University Hospital Medical Information Network—Clinical Trial Registry) with the number C000000001.

Statistical analysis

Analysis of the intent to treat principle was applied to the statistical analysis. Efficacy analysis uses a full analysis set (FAS), and all of the enrolled patients are applied to the analysis except for patients without efficacy data, patients who do not correspond to inclusion criteria and patients who do not receive treatment. The PPS (protocol per set) group is defined as consisting of patients without any serious protocol violation.

Recruitment of the practitioner

The explanatory meeting of the protocol and registration was held in all of Japan. The executive members of the A-TOP research group were responsible for the presentation of the protocol and for the recruitment of study institutions and practitioners. The A-TOP committee created the WEB site on the Internet so that the registration of the study could be executed directly. I'cros Co., Ltd., was also involved as a collaborator in calling practitioners.

Results and discussion

Several principles had to be considered for acceptance of concurrent treatment: firstly, the concurrent treatment should be clinically and statistically significantly more effective than the basic treatment; secondly, the concurrent treatment should be of the same level of safety as single treatment; thirdly, the concurrent treatment should be cost-effective. Although these principles should be evaluated before adopting concurrent treatment, the authors have applied concurrent treatment to osteoporosis widely, without any background evidence. Among these principles, the authors have decided to evaluate the first two issues, effectiveness and safety, in the present study. Since this type of evaluation is absolutely required by a clinician, a researcher-initiative study was considered as being the most suitable type of evaluation. This was the reason why the authors decided to use a researcher-initiative clinical trial in determining the effectiveness of concurrent treatment for osteoporosis. The JOINT-02 protocol was the first randomized, controlled trial conducted nationwide for osteoporosis in Japan initiated by researchers, and its scale was also the largest ever. It was therefore necessary for various organizations to collaborate together, and there

have been no previous reports on how to manage the PROBE trial in Japan. This is why we wanted to report the design of JOINT-02. In this paper, we have presented the organization of the A-TOP research group and execution of the JOINT 02 protocol. This is because we believe that this report should help a researcher who is willing to build a new nationwide investigation that is constructed by an organization of clinical research work.

Since the primary aim of JOINT-02 was to determine whether concurrent treatment using ALN and alfacalcidol is superior to treatment using ALN alone in terms of fracture prevention, true ("hard") endpoints such as vertebral fractures or long bone fractures were selected as the primary endpoint. The diagnosis of whether vertebral fractures were present or not on the X-ray films was made by two independent reviewers who did not have any information about the patient; when the judgment of fractures was split between the two reviewers, the reviewers negotiated with each other. Identifying vertebral fractures is more difficult than identifying long bone fractures due to some cases of new vertebral fractures not showing clinical symptoms and the shape of the vertebral body making it difficult at times to recognize whether there is a fracture. Therefore, to avoid misdiagnosis, diagnosis of pre-existing and incident vertebral fractures was made by two different observers. In cases where there was a discrepancy in the diagnosis of vertebral fractures between the reviewers and the practitioner, which occurred with regard to pre-existing fractures, the reviewers' judgment was given priority over that of the practitioner.

Surrogate ("soft") endpoints such as change in BMD or bone turnover markers were considered to be inadequate as primary endpoints in making conclusive statements regarding the efficacy of concurrent treatment. In this type of study, the soft endpoint (BMD or biomarkers) will connect dropout bias less effectively than the case-selected hard endpoint, because such markers are not able to be made blind to the clinicians. Furthermore, previous studies indicate that changes in BMD or bone markers do not predict future fractures [22–24].

In recent literature, it has been reported that poor adherence of bisphosphonates leads to a decline in the beneficial effects of this drug on bone [25–28]. It is expected that in contrast to prior developmental trials, this current study may have a higher dropout rate, since in a researcher-initiative study, the registered practitioner is not forced to maintain adherence very strictly. As a result, adherence in the present study may resemble the actual circumstances of adherence to bisphosphonate treatment by a general practitioner. It will be interesting to determine whether adherence in this study modifies fracture prevention by alendronate.

Although a careful plan for this study has been set up, the results will be applied to osteoporosis patients with the same background as the present study population, but not adapted to the entire osteoporosis population. Despite this limitation, we believe that the results will give us very important information regarding the concurrent treatment of osteoporosis.

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The Fracture and Immobilization Score (FRISC) for risk assessment of osteoporotic fracture and immobilization in postmenopausal women—A joint analysis of the Nagano, Miyama, and Taiji Cohorts

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ABSTRACT

Introduction: We aimed to (i) explore risk factors for major osteoporotic fracture or immobilization; (ii) develop a prediction model that can be used to assess the risk of fracture and immobilization; and (iii) assess external validity of the final model.
Methods: A total of 1787 postmenopausal Japanese women were followed in a hospital-based cohort study. Endpoints included the annual incidence of major osteoporotic fracture and immobilization. For each endpoint, multivariate Poisson regression models were fitted separately and risk factors were screened through backward variable selection. The predictive accuracy of the final model (FRISC) was evaluated in two independent community-based cohorts.
Results: Over a median follow-up of 5.3 years, a total of 383 major osteoporotic fractures (279 clinical vertebral, 44 hip, 60 distal forearm) and 83 immobilizations occurred in the developmental dataset. Backward variable selection confirmed that the following are risk factors for major osteoporotic fracture: age, weight, prior fracture, back pain, and lumbar bone mineral density (BMD). Age, prior fracture and dementia were significant risk factors for immobilization. Hosmer–Lemeshow tests did not indicate any significant deviation between the observed fracture frequency and prediction from the FRISC in the independent validation dataset. The C statistic for the FRISC was 0.727 (95% confidence interval: 0.660 to 0.794) and was higher than that for BMD alone significantly ($p = 0.03$).
Conclusions: We developed a novel prediction model for fracture and immobilization, FRISC, and the clinical risk factors in the FRISC allows better identification of populations at high risk of fracture than BMD alone. A web application is available at http://www.biostatistics.jp/prediction/frisc.

Introduction

Fracture due to osteoporosis results in increased mortality, morbidity and medical expense in the US and Japan [1–3]. As an adjunct to the development of effective treatments, early identification of populations at high risk of fracture is regarded as an effective strategy for decreasing both the burden of illness and the associated cost in countries with aging populations [4]. The US and Japanese guidelines both recommend that bone mineral density (BMD) should be used to determine when to intervene in patients with osteoporosis [5,6]. However, epidemiological studies have demonstrated that many major osteoporotic fractures occur among individuals with a BMD T score value above the intervention threshold value, although the incidence of fracture certainly increases with decreasing BMD [7,8]. As a solution to this problem, a WHO scientific group proposed the use of 10-year probabilities of osteoporotic or hip fracture, calculated using multiple risk factors. The result was the WHO fracture risk assessment tool (FRAX) [9]. Several other prediction models/risk assessment tools were also developed based on data from cohort studies and clinical trials [10–13].

Abbreviations: BMD, bone mineral density; FRAX, fracture risk assessment tool; FRISC, Fracture and Immobilization Score; CHD, coronary heart disease; CVD, cerebrovascular disease; ROC, receiver operating characteristic; CI, confidence interval.

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Although case-finding strategies optimized by risk assessment tool for fracture appear to be promising, there are several problems which must be addressed before clinical application. First, whether combination of BMD and clinical risk factors allows better discrimination of fracture than BMD alone is still controversial; the discriminatory power of the FRAX was excellent in eleven population-based cohorts [14] but was similar to BMD alone in a cohort study [15]. Second, since the Japanese version of FRAX was validated only in the community dwelling cohorts in Japan [9], there has been no available data whether the FRAX probability performs well in hospital-based population. As Justice et al. pointed out, the effectiveness of prediction models in clinical practice depends on the extent to which they can be generalized to the population in question [16]. In general practice, the FRAX was often adapted to assess fracture risk in a patient who has a more complicated risk for fracture, such as atherosclerosis, diabetes or other potential risks to deteriorate bone strength. In this regard, it is necessary to evaluate prediction models for fracture not only in community but also hospital-based populations. Third, outcomes other than fracture, such as immobilization, appear to be also important for optimizing osteoporotic treatment from the health economic perspective. In fact, we have found that osteoporotic fracture was an independent risk for immobilization and this morbid state would require a large amount of resources of care [17].

The present study was therefore performed with three main aims. The first was to explore risk factors for the incidence of major osteoporotic fracture or immobilization. This was done using data from the Nagano Cohort, a hospital-based cohort study of postmenopausal Japanese women. The second aim of this study was to develop a prediction model named as the Fracture and Immobilization Score (FRISC), to assess the risk of major osteoporotic fracture and immobilization, based on the risk factors confirmed in the first part of the study. Finally, we assess the external validity of the FRISC and investigate whether the predictive accuracy was improved from BMD alone using pooled data from the Miyama and Taiji Cohorts, which followed 400 Japanese women from communities over a 10-year period.

Methods

Development and validation datasets

We used two independent datasets in the current analysis; a developmental dataset from the Nagano Cohort and a validation dataset from the Miyama and Taiji Cohorts. Profiles of these three cohorts have been detailed previously [17–28]. The Nagano Cohort recruited and followed up postmenopausal women who were receiving medical care as outpatients or visitors at a medical institute in Nagano Prefecture, Japan since April 1993 [16–20]. A total of 1787 participants were included in the developmental dataset; exclusion criteria were (i) metabolic bone disease and (ii) secondary osteoporosis (e.g. hyperparathyroidism, hyperthyroidism other than patients on T4 replacement and with euthyroid for more than one year, chronic renal failure or osteomalacia). We excluded those who met the exclusion criteria regardless of BMD.

However, steroid users were enrolled to the present study because the history of steroid use was required in the FRAX. The protocol was approved by the ethics committee at the Research Institute and Practice for Involutional Diseases and we obtained written informed consent from all participants. The Miyama Cohort was set up in 1988 as subsets of nationwide community-based cohort studies sponsored by the Ministry of Education or Ministry of Health and Welfare [21–23]. A total of 1453 inhabitants aged 40–79 years in Miyama Village were listed from the resident registration in December 1988. Then, 200 men and 200 women were recruited and followed up between 1990 and 2000. The Taiji Cohort is a community-based cohort study in Taiji Town, Wakayama Prefecture, Japan [25–27]. From a list of 2261 inhabitants aged 40–79 years obtained from the resident registration in June 1992, 50 men and 50 women in each decade age group between 40 and 79 years (a total of 400 participants) were recruited randomly and followed up between 1993 and 2003. All the sampled participants were contracted and agreed to participate. The validation dataset included all the women in the Miyama and Taiji Cohorts.

Data collection in the Nagano Cohort

At baseline, anthropometric indices, including body weight and body height, were obtained for all patients. Subjects were also interviewed to obtain data about age at menopause, smoking habit, alcohol consumption, past and present occupation, presence of pain, medical history (including rheumatoid arthritis, diabetes mellitus, hypertension, dyslipidemia, cancer, dementia, coronary heart disease [CHD] and cerebrovascular disease [CVD]). Pain was defined as any symptom of pain in the back, hip muscles, ribs, legs, knees, neck, shoulders, wrists, or other joints. Back pain was defined as any symptom of pain in the back trunk area, regardless of the degree or consistency of the pain [18]. Rheumatoid arthritis was diagnosed according to the diagnostic criteria proposed by the American Rheumatism Association [28]. The Japanese version of the Mini-mental State Examination (MMSE) was performed in the subjects who were suspicious dementia and a subject with the total score of MMSE less than 20 points was considered to have obvious cognitive dysfunction [29]. A history of CHD was defined as any previous acute coronary symptoms or events requiring coronary intervention, and was confirmed by coronary angiography, echocardiogram, or MD-CT imaging study. A history of CVD was diagnosed based on evidence of apparent brain attack or an existing brain lesion as observed by magnetic resonance imaging or computer-assisted X-ray tomography. Self-reports of a history of malignancy were confirmed by referring to the patient's medical records [19]. The BMD of the lumbar spine was measured at baseline using dual-energy X-ray absorptiometry (Lunar DPX-L or DPX-IQ; Lunar Corporation, Madison, WI) and a quality assurance test was carried out for every measurement to detect machine drift. The inter-assay variance of the lumbar BMD measurements in our laboratory was $0.5 \pm 0.5\%$ (coefficient of variation $\pm$ standard deviation) [20]. T score was calculated by using Japanese standard values [30].

Data collection in the Miyama and Taiji Cohorts

A self-administered questionnaire was used for baseline data collection in the Miyama Cohort, while both self-administered and interviewer-administered questionnaires were used in the Taiji Cohort [22–27]. The items in these questionnaires included birth date, body weight, body height, current smoking status, current alcohol intake, presence of back pain, use of steroids, and medical history such as rheumatoid arthritis. Parental history of fracture was asked only in the Taiji Cohort. The BMD of L2-4 and BMD at femoral neck, Ward's triangle and the trochanteric region were measured by dual-energy X-ray absorptiometry (Lunar DPX; Lunar Corporation, Madison, WI in the Miyama Cohort, Hologic QDR-1000; Hologic Inc., Crosby Drive Bedford, MA in the Taiji Cohort) and treated as T scores. The incidence of clinical fracture was evaluated in both the cohorts. However, radiographs for morphometrical vertebral fracture were available only in the Miyama Cohort. Consequently, parental history or morphometrical vertebral fracture was missing data in either cohort systematically and thus we assumed that participants with these missing data did not have parental history or prior fracture. We calculated the 10-year probability of major osteoporotic fracture by entering the following data into online version of the FRAX; age, sex, weight, height, previous fracture, parental history of hip fracture, current smoking status, glucocorticoid use, rheumatoid arthritis, alcohol intake and femoral neck BMD.

Endpoints

Endpoints included the annual incidence of major osteoporotic fracture and immobilization. Major osteoporotic fracture was defined

as first occurrence of any clinical fracture (hip fracture, surgical neck fracture of the humerus, distal forearm fracture, or clinical vertebral fracture). We also evaluated a radiographical vertebral fracture by the semi-quantitative visual method [31], but major osteoporotic fracture does not include morphometrical fracture by definition. A validation analysis of our semi-quantitative method for analyzing incident vertebral fracture has been reported elsewhere [32]. Prior vertebral fractures were defined as those fractures for which the ratio of the height of the central or anterior vertebral body to that of the posterior vertebral body was less than 0.8, or when any of these three vertebral body heights was less than 80% of the height of the adjacent vertebral body [6]. Immobility was defined in accordance with the subject's locomotive ability. Subjects bed-bound at home (lying in bed almost all day) for more than 6 months or institutionalized in nursing homes (lying in bed or using a wheelchair for locomotion), were defined as immobile [17]. Some immobile subjects could be sitting on a bed and could be going to a portable toilet which located besides the bed. Participants who died from any cause, moved to the home of a relative because they were not able to perform the activities of daily living independently, were lost to follow-up, or were followed up until June 1, 2009 were treated as censored. For each endpoint, the accumulation of person-years at risk started from registration of each patient.

Statistical considerations

For each endpoint, we fitted multivariate Poisson regression models separately and rate ratios for risk factors estimated by the Poisson regression models were reported with 95% confidence intervals (CI) and p values. The following variables were initially identified from the literature as the traditional risk factors for osteoporotic fracture: covariates included in the FRAX other than femoral neck BMD (age, height, weight, prior fracture, parental history of fracture, current smoking status, use of steroids, rheumatoid arthritis, alcohol intake), lumbar BMD, presence of back pain, presence of any pain, and drug treatment for osteoporosis [9,18,22]. These covariates were screened via backward variable selection with a significance level of $p=0.2$. We constructed a prediction model for immobilization using the same procedure, except that three covariates (dementia, history of CVD, and history of malignancy) were used in addition to those used in the osteoporotic fracture analysis. Finally, the FRISC was developed using the following formula:

$$\mathrm{Prob}(t) = \int_0^t \lambda \exp(\mathbf{X}\boldsymbol{\beta}) \exp\left[-\int_0^u \{\lambda \exp(\mathbf{X}\boldsymbol{\beta}) + m(v)\} dv\right] du$$

Here, t is a time point for prediction (i.e. the formula calculates 10-year probability if $t=10$), $\boldsymbol{\beta}$ is a vector of log-rate ratios for covariates $\mathbf{X}$, λ denotes baseline incidence rate, and $m(v)$ is mortality at time v obtained from sex- and age-specific mortality in Vital Statistics of Japan in 2008 [33].

We assessed the predictive accuracy of the FRISC in terms of calibration and discrimination [34] using occurrence of major osteoporotic fracture within a 10-year period, which was treated as a binary event, in the validation dataset. Calibration, namely how closely the prediction reflects actual events, was assessed using ratio of observed and predicted events and the Hosmer–Lemehshow test. Discrimination, the ability to distinguish between those who experience the event and those who do not, was evaluated using receiver operating characteristic (ROC) curves and Harrell's C statistic. Improvement in the C statistics of the two models from BMD alone was assessed by using contrast tests.

All reported p values for statistical tests are two-tailed, and $p<0.05$ was taken to indicate statistical significance. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Characteristics of participants and follow-up

Baseline characteristics of participants in the Nagano, Miyama and Taiji Cohorts are summarized in Table 1. The Nagano Cohort included older participants and mean lumbar BMD in this cohort was lower than the other cohorts. Prior fracture, back pain and parental history were observed more frequently in the Miyama and Taiji Cohorts. In the Nagano Cohort, 37.4% of participants were being treated with bone resorption inhibitors (bisphosphonates or a selective estrogen receptor modulator), and 16.7% were receiving 1-alpha-OH vitamin D_3 or vitamin K_2 at baseline. Table 2 describes the incidence of fractures and immobilization. In the Nagano Cohort, over a median follow-up time of 5.3 years (range, 0.03–16.5 years), a total of 383 major osteoporotic fractures occurred (279 clinical vertebral fractures, 44 hip fractures, 60 distal forearm fracture, Table 2). In the Miyama and Taiji Cohorts, 337 of 400 participants completed the planned follow-up of the 10-year period (84%) and a total of 60 major osteoporotic fractures occurred (44 clinical vertebral fractures, 8 hip fractures, 8 distal forearm fracture, Table 2). Incidence rates of fractures in the two cohorts were much lower than the Nagano Cohort possibly due to the difference in average age and lumbar BMD at baseline (Tables 1 and 2). Immobilization occurred in 83 participants in the Nagano Cohort.

Risk factors for fracture and immobilization

We fitted multivariate Poisson regression models to the validation dataset of 1787 participants. Backward variable selection identified the following six risk factors for major osteoporotic fracture: age, weight, lumbar BMD, prior fracture and presence of back pain (Table 3). That is, parental history of fracture, smoking status, alcohol consumption, rheumatoid arthritis, and use of steroids, which are all

Table 1
Characteristics of participants in the three cohorts.

	The Nagano Cohort (N = 1787)			The Miyama and Taiji Cohorts (N = 400)		
	Mean	SD	5–95 percentile	Mean	SD	5–95 percentile
Age (years)	63.4	11.1	45–81	59.5	11.3	41–77
Height (cm)	150.9	6.6	140–161	150.2	6.2	140–159
Weight (kg)	51.1	8.5	38–65	51.2	9.3	37–66.5
Lumbar BMD (T score)	−1.55	1.22	−3.5–0.5	−1.36	1.19	−3.85–1.57
Femoral neck BMD (T score)	*			−1.61	1.84	−3.29–0.53
			Frequency	%	Frequency	%
Prior fracture			403	22.6	49†	25.0
Presence of pain	Back		572	32.0	251	63.0
	Other sites		449	25.1	†‡	
Parental history			22	1.2	20‡	10.0
Current smoker			38	2.1	16	4.0
Current alcohol drinker			137	7.7	46	11.5
Medication	Bone resorption inhibitors		369	37.4	†‡	
	Active vitamin D_3 or vitamin K_2		299	16.7	†‡	
	Steroids		27	1.5	0‡	0.0
Rheumatoid arthritis			224	12.5	0	0.0
Dementia			97	5.4	†‡	

SD: standard deviation; BMD: bone mineral density.
*Not measured in the Nagano Cohort. †Not measured in the Miyama Cohort (N = 200).
‡Not measured in the Taiji Cohort (N = 200).

Table 2
Frequencies and incidence rates of fracture and immobilization in participants in the three cohorts.

	The Nagano Cohort (N = 1787)				The Miyama and Taiji Cohorts (N = 400)			
	Frequency	IR	95% CI		Frequency	IR	95% CI	
Major osteoporotic fracture	383	34.1	30.9	37.7	60	16.1	12.5	20.7
Clinical vertebral facture	279	24.9	22.1	28.0	44	11.8	08.8	15.9
Hip fracture	44	3.9	2.9	5.3	8	2.2	1.1	4.3
Immobilization	83	7.4	6.0	9.2	-			

IR, incidence rate per 1,000 person-years; CI, confidence interval.

included in the FRAX, were excluded based on having p values less than 0.2. Importantly, incidence rate of major osteoporotic fracture increased as weight elevated and this direction is opposite to the FRAX and this trend remains significant even when all the other risk factors listed initially in the variable selection procedure are adjusted for (rate ratio for 10 kg increase in weight: 1.22, 95% CI: 1.07 to 1.40, $p<0.01$). Multivariate analysis for immobilization, using the same variable selection procedure, showed that age, prior fracture and dementia were associated with the incidence of immobilization (Table 3).

Input and output of the FRISC

All the risk factors that were retained through the variable selection procedure were incorporated into the final prediction model named as the FRISC. Interface of web application of the FRISC is displayed in Fig. 1. The input comprises the sex risk factors and, menopausal status and secondary osteoporosis which were used only for assessment of the applicability. The output comprises the 1, 3, 5 and 10-year probabilities of major osteoporotic fracture and those of immobilization and is calculated by using the algorithm described in Supplementary Data.

External validation of the FRISC

Fig. 2 displays histograms of the calculated 10-year probabilities of major osteoporotic fracture for the 400 participants in the validation dataset (upper: the FRISC, lower: the FRAX). An apparent difference was observed in the left tail of the two histograms; in the upper figure participants with fracture probability less than 0.05 were very few, while the FRAX gave the fracture probability less than 0.05 to a substantial portion of the participants. As a result, the fracture probabilities from the FRISC were much higher on average. Table 4 compares the predictive accuracy of the two prediction models and prediction from BMD alone. Over the 10-year follow-up, major osteoporotic fracture developed in 60 of 400 participants in the validation dataset. The predicted event frequency calculated from the FRISC was slightly higher than the observation (observed/predicted ratio: 0.74), while the FRAX tended to underestimate (observed/predicted ratio: 1.59). The Hosmer–Lemeshow test did not indicate any significant deviation between the observed event frequency and prediction from the FRISC. The C statistics for the FRISC was 0.727, indicating that the discriminatory power of the FRISC is moderate, while that for prediction from BMD alone was 0.651. That is, the discriminatory power of the FRISC, which combines BMD and additional clinical risk factors, was better than BMD alone significantly even in independent community-based cohort studies ($p=0.03$, Table 4). Fig. 3 shows ROC curves for major osteoporotic fracture probability from the FRISC (solid curve), the FRAX (dashed curve) and BMD alone (dotted curve). Both the ROC curves of the prediction models increased almost identically at first, but the curve for the FRISC was slightly above the curve for the FRAX where sensitivity is higher than 0.7 and where lower probability is used as a cutoff point (i.e. 16% or lower in the FRISC, 14% or lower in the FRAX), indicating that the FRISC is advantageous over the FRAX for screening of low-risk osteoporotic patients.

Table 3
Multivariate Poisson regression analysis of risk factors for major osteoporotic fracture and immobilization in the development dataset of 1,787 participants.

	Major osteoporotic fracture				Immobilization			
	Rate ratio	95% CI		p	Rate ratio	95% CI		p
Age, + 10 years	1.62	1.43	1.83	<0.01	2.80	2.09	3.73	<0.01
Weight, + 10 kg	1.25	1.10	1.42	<0.01	-	-	-	-
Lumbar BMD, + 1 T score point	0.85	0.76	0.94	<0.01	-	-	-	-
Prior fracture, yes/no	2.00	1.57	2.54	<0.01	2.04	1.21	3.44	0.01
Back pain, yes/no	1.58	1.27	1.96	<0.01	-	-	-	-
Dementia, yes/no	-	-	-	-	2.09	1.32	3.29	<0.01

BMD: bone mineral density; CI: confidence interval.

Discussion

In the current study, we explored clinical risk factors for major osteoporotic fracture and immobilization and developed a novel prediction model, the FRISC. Importantly, the assessment of external validity showed that the FRISC allows accurate prediction of major osteoporotic fracture even in the community-based setting and after a long-term follow-up of ten years, although it was developed in a hospital-based cohort study (i.e. for outpatients and visitors to a clinic). Therefore, the FRISC is useful both not only for patients who have a more complicated risk for fracture, such as atherosclerosis, diabetes or other potential risks to deteriorate bone strength, but also general postmenopausal women. Further the discriminatory power of the FRISC was shown to be better than BMD alone. We have previously noted that there is a close relationship between bone fractures and subsequent immobilization in postmenopausal Japanese women, and that these two conditions are morbid states that require a large amount of health resources [17]. Therefore, an accurate measure to predict these two conditions is particularly valuable in the context of an aging society. A web application of the FRISC is available at http://www.biostatistics.jp/prediction/frisc (Fig. 1).

The major finding of the current study is that inclusion of the four clinical risk factors, namely age, weight, prior fracture and back pain, in addition to BMD significantly improved the accuracy of the prediction model for major osteoporotic fracture. In contrast, parental history of fracture, smoking status, alcohol consumption, rheumatoid arthritis and use of steroids, which are all included in the FRAX, were not associated with incidence of fracture in the present analysis. The reason for this observation does not appear to be a lack of power given the number of observed events in the Nagano Cohort. Diet and other lifestyle factors, which were Westernized among smokers in this cohort, may have contributed to this unexpected result. One implication of these findings is that the association between lifestyle factors and fracture risk is possibly biased due to confounding factors, and it is necessary for prediction models to reflect the multidimensional nature of lifestyles. Although there were smokers and drinkers in the present population, the extent of their smoking and drinking was very mild, and smaller percentages of patients had these habits than in comparable Caucasian populations. In the practical point of view, a more parsimonious model is desirable and the FRISC would therefore provide a simple but sufficiently accurate measure for prediction of major osteoporotic fracture.

The present results indicated that incidence of fracture increases with heavier body weight, although low BMI has been considered as a significant risk factor of fracture as proposed in the FRAX. This trend remained even after the adjustment for the other risk factors

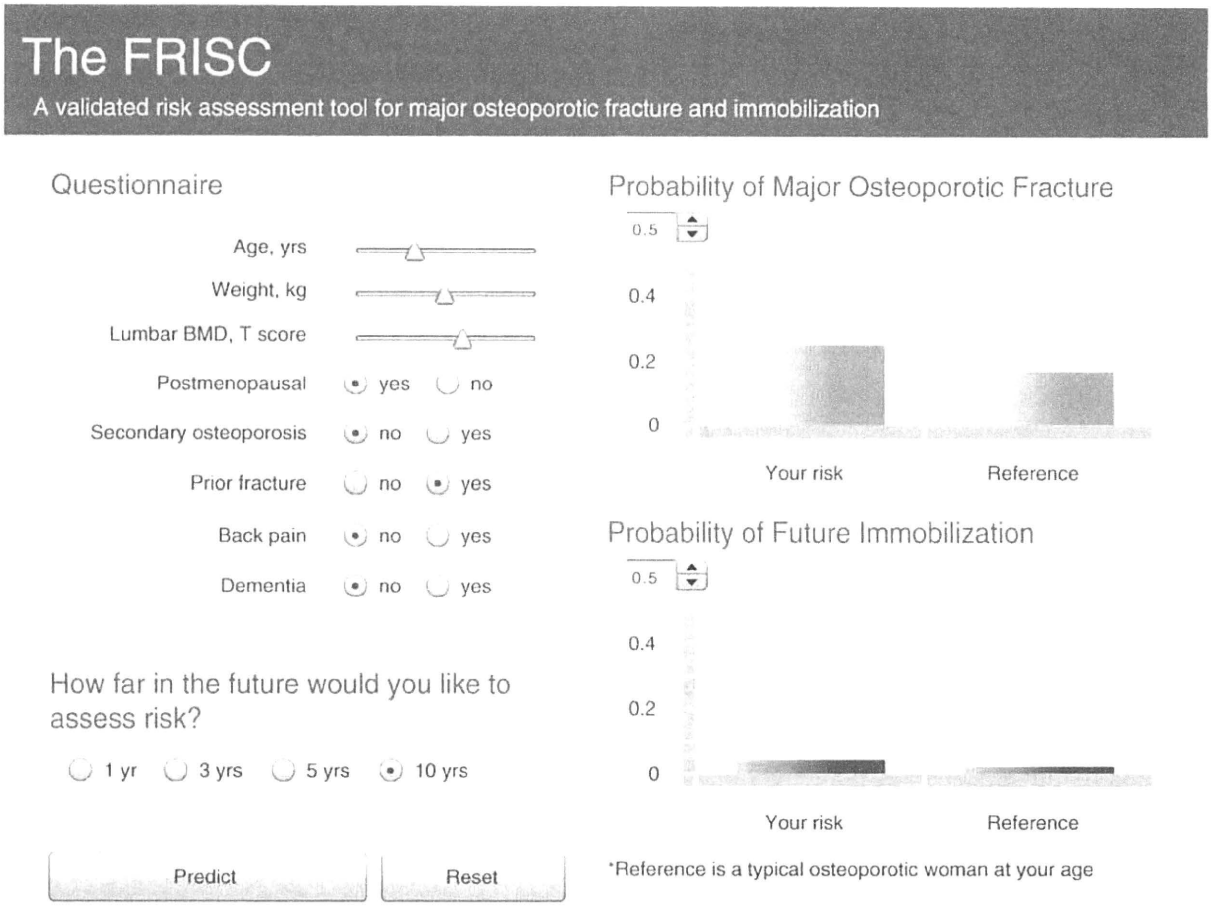

Fig. 1. Input and output of the web application of the FRISC.

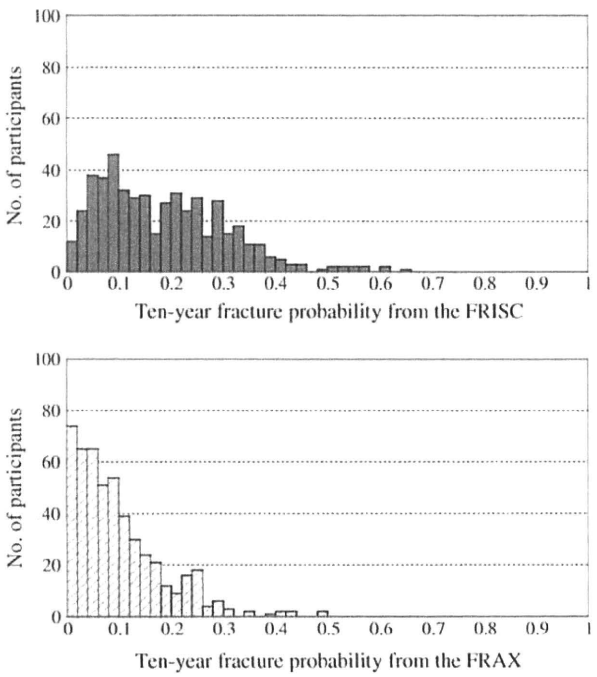

Fig. 2. Histogram of 10-year probabilities of major osteoporotic fracture from the FRISC (upper) and the FRAX (lower) in the Miyama and Taiji Cohorts.

(p<0.01) and therefore seemed to be attributable to confounders. This may be one of the causes of discrepancy in 10-year probability between the FRAX and the actual fracture rate in the three cohorts. Recent report indicated that morbid obesity had a higher susceptibility of fractures comparing to the postmenopausal women with normal weight although the BMD of the obesity was higher than the controls [35]. As it is well known that obesity will connect to have diabetes mellitus or at least to have glucose intolerance and diabetes may deteriorate bone quality due to an increase in non-enzymatic glycation induced cross-links of collagen, which increased collagen

Table 4
Predictive accuracy of major osteoporotic fracture probability from the FRISC compared the FRAX evaluated in the validation dataset from general population.

	Calibration			Discrimination			
	Predicted no. of cases	Observed/predicted ratio	p^*	C statistics[†]	95% CI		$p^‡$
BMD alone	–	–	–	0.651	0.575	0.728	–
The FRAX	37.8	1.59	<0.01	0.699	0.629	0.768	0.23
The FRISC	81.2	0.74	0.17	0.727	0.660	0.794	0.03

CI: confidence interval.

* Hosmer–Lemeshow test, p value less than 0.05 indicates a significant deviation between the observed and predicted event frequencies. Number of strata and degree of freedom are 10 and 8, respectively.

† The proportion of all patient pairs in which prediction and observed occurrence of event are concordant.

‡ Contrast test comparing C statistics of the FRAX and FRISC from that of BMD alone, p value less than 0.05 indicates a significant improvement from BMD alone.

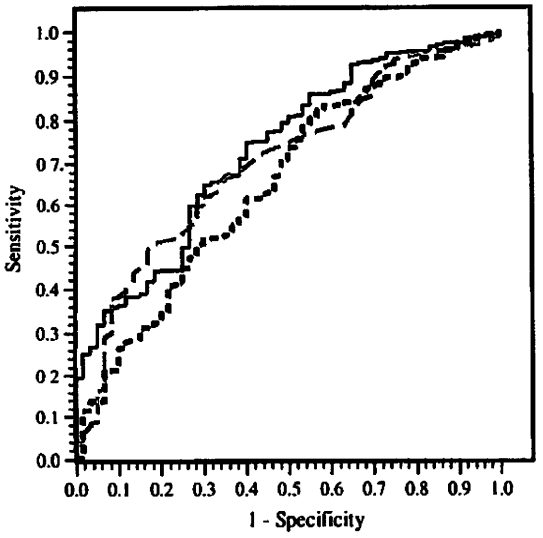

Fig. 3. Receiver operating characteristic curve for major osteoporotic fracture probability from the FRISC (solid curve), the FRAX (dashed curve) and BMD alone (dotted curve) in the Miyama and Taiji Cohorts.

brittleness [36,37]. Lifestyle factors such as diet and exercise may also be other explanations for this observation.

Although the intrinsic properties of the bone are important components of fracture risk, assessment of these factors alone does not adequately reflect the full range of factors associated with the occurrence of fracture [38]. Loss of bone mass and impaired bone quality are commonly held to be the two major causes of increased bone fragility in osteoporosis [2]; however, existing prediction models do not directly take bone quality into consideration. Despite recent progress in understanding the composition and structure of the bone, there are currently no standard assessments of bone quality. Novel bone quality-related markers such as homocysteine [39,40] and pentosidine [41] appear to improve predictive accuracy, but further research is required to determine whether they will be useful in the context of predicting osteoporotic fracture.

The incidence of clinical vertebral fracture in the Japanese population is substantially high (Table 2). As a result, the 10-year fracture probabilities generated using the FRISC is much higher than the FRAX (Fig. 2). The major underlying cause of the discrepancy in the 10-year probabilities is likely to be the difference in population. The FRISC was developed in a cohort study conducted at one medical institute and included subjects who were receiving treatment for osteoporosis, whereas the FRAX was developed using data from a community-based population. Although the effectiveness of bisphosphonate and selective estrogen receptor modulators in reducing fracture risk has been demonstrated, in the current analysis, drug treatment for osteoporosis was not a significant factor at the site of major osteoporotic fracture after adjustment for other risk factors, suggesting that its influence on risk is smaller than that of the risk factors. People who visit a hospital or clinic possibly have a higher prevalence of co-morbid conditions than people in the general population, yielding an increased incidence of fracture because of deterioration in both bone quality and quantity.

Given the large difference in incidence rates of fracture between the Nagano Cohort and the Miyama and Taiji Cohorts (Table 2), it may not seem to be sensible to choose the Miyama and Taiji Cohorts as validation cohorts since a good fit is unexpected. However, as shown in Table 1, the Nagano cohort included older participants and the mean lumbar BMD in this cohort was lower than the other cohorts. Therefore the difference in participants' characteristics may be attributable to the higher incidence rate in the Nagano cohort relative to the other cohorts. Further, the Miyama and Taiji Cohorts followed participants over a 10-year period and are more suitable for the validation analysis. A limitation of our validation analysis was that parental history or morphometrical vertebral fracture was missing data in either of the validation cohorts systematically. We assumed that participants with these missing data did not have parental history or prior fracture, yielding a somewhat lower 10-year probability of major osteoporotic fracture. Given that we did not find any evidence of deviation between the observed fracture frequency and prediction from the FRISC even in independent community-based cohort studies, the FRISC appears to allow accurate prediction of major osteoporotic fracture both in community-based and hospital-based settings.

Supplementary materials related to this article can be found online at doi:10.1016/j.bone.2010.08.019.

Conclusion

We developed a novel prediction model for fracture and immobilization, FRISC, and the clinical risk factors in the FRISC allows better identification of populations at high risk of fracture than BMD alone.

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一般住民における動脈硬化と骨粗鬆症の関連

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一般住民における動脈硬化と骨粗鬆症の関連

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はじめに

骨粗鬆症と動脈硬化の進行は，高齢者の自立を障害してquality of life(QOL)を低下させ，健康寿命に大きく影響する。これら両疾病はともに，加齢に伴い発症・増加する病態である。

骨密度(bone mineral density：BMD)と循環器疾患の関連については，これまでにも多方面からの研究報告が数多くあるが，日本人地域住民男女を対象としての疫学研究はまだ少ない。本研究では，地域在住中高年者を対象に，骨粗鬆症と動脈硬化の関連について横断的に検討を行った。

1　対象と方法

国立長寿医療センター研究所疫学研究所では，老化に関する包括的な疫学調査である「国立長寿医療センター研究所・老化に関する長期縦断疫学研究(NILS-LSA：National Institute for Longevity Sciences-Longitudinal Study of Aging)」を，1997年11月から縦断的(2年ごと)に実施している[1)]。調査対象は，センター周辺(愛知県大府市，知多郡東浦町)の地域住民から，年齢，性別で層化した無作為抽出法で選出された，ベースライン調査時年齢が40～79歳の2,267名である。

本研究では，第1次調査(1997年11月～2000年4月)の参加者のうち，BMD測定および頸動脈超音波検査を受けた女性1,050名(平均年齢±SD：59.0±10.9)，男性1,063名(59.2±10.9)を対象として横断研究を行った。**表1**に対象者特性を示す。

骨粗鬆症の評価は，dual energy X-ray absorptiometry(DXA：Hologic, QDR-4500)で第2～4腰椎と右大腿骨頸部のBMD測定を行い，日本骨代謝学会の「原発性骨粗鬆症の診断基準」[2)]に準じ，BMDが若年成人平均値(young adult mean：YAM)の70～80％を骨量減少，

表1　対象者特性

	男性	女性
対象者数(名)	1,063	1,050
40歳代	274	266
50歳代	267	266
60歳代	255	263
70歳代	267	255
年齢(歳)	59.2±10.9	59.0±10.9
BMI(kg/m^2)	22.9±2.8	22.9±3.3
腰椎BMD(g/cm^2)	1.0±0.2	0.9±0.2
大腿骨頸部BMD(g/cm^2)	0.8±0.1	0.7±0.1
IMT(mm)	0.9±0.5	0.8±0.3

平均値±標準偏差
BMI：body mass index, BMD：bone mineral density, IMT：intima-media thickness

Association between Arteriosclerosis and Osteoporosis in Community Dwelling Population
Marie Takemura：Department of Orthopedics National Center for Geriatrics and Gerontology, *et al.*
Key words：Osteoporosis, Arteriosclerosis, Epidemiology

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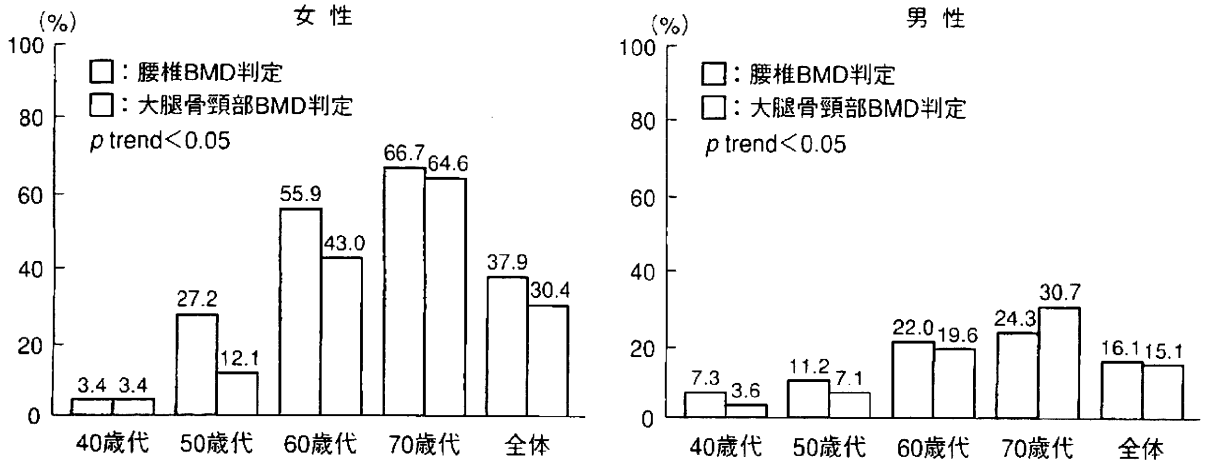

図1　骨粗鬆症/骨量減少の有病率

70%未満を骨粗鬆症と判定した。

また，動脈硬化の評価手段として頸動脈超音波検査(日立メディコ電子走査形超音波断層装置EUB-655，電子リニア形探触子EUP-L3 10MHz)を行った。頸動脈内膜中膜複合体厚(intima-media thickness：IMT)を左右総頸動脈および左右頸動脈分岐部で計測し，その最肥厚部をIMTの代表値とした。IMTが1.1mm以上を異常肥厚とし，動脈硬化ありと判定した。

統計学的検討として，骨粗鬆症および動脈硬化の地域在住中高年者の有病率を性別，年代別に求め，Cochran-Mantel-Haenszel法によるトレンド検定を行った。次に動脈硬化と骨粗鬆症の関連について検討するために，動脈硬化の有無を説明変数とし，年齢およびbody mass index(BMI)を調整した骨粗鬆症有病についての多重ロジスティック回帰分析を性別に行った。解析には，統計プログラムSAS release 9.1.3を使用した。

2　結　　果

1) 骨粗鬆症/骨量減少の有病率(性別，年代別)

腰椎BMD判定での40歳以上の骨粗鬆症/骨量減少の有病率は，女性37.9%，男性16.1%であった。女性の有病率は加齢で有意に高くなり，特に60歳代以降は急速に高くなった。男性でも，有病率は加齢で有意に高くなった。大腿骨頸部BMD判定でも，女性30.4%，男性15.1%で，男女とも加齢で有意に高くなった(**図1**)。

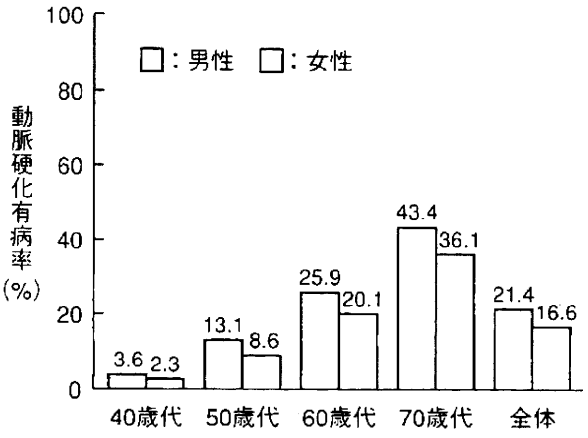

図2　動脈硬化有病率

2) 動脈硬化有病率(性別，年代別)

40歳以上の女性の動脈硬化有病率は16.6%，男性は21.4%であった。動脈硬化の有病率は，男女とも加齢で有意に高くなった(**図2**)。

3) 動脈硬化と骨粗鬆症との関連

女性で骨粗鬆症診断を腰椎BMDで判定した場合，動脈硬化のある者は，ない者に比べて骨粗鬆症/骨量減少の有病の割合が高かった(オッズ比1.97，95%信頼区間1.03～2.99，$p=0.0014$)。また，女性を未閉経群と閉経群に分けて検討したところ，閉経群のみで同様の結果が得られた(1.78，1.19～2.67，$p=0.00052$)。一方，大腿骨頸部BMD判定の場合には，いずれも有意な関連は認められなかった。男性での解析では，両部位BMDと動脈硬化のあいだに有意な

表2　多重ロジスティック回帰分析による動脈硬化と骨粗鬆症有病の関連

		オッズ比(95%信頼区間)	p値
腰椎BMD判定の場合	女性全体	1.97(1.03～2.99)	$p=0.0014$
	閉経女性	1.78(1.19～2.67)	$p=0.0052$
	男性全体	0.98(0.63～1.55)	NS
大腿骨頸部BMDの場合	女性全体	0.96(0.63～1.46)	NS
	閉経女性	0.94(0.60～1.43)	NS
	男性全体	0.74(0.27～1.17)	NS

NS：not significant

関連は認められなかった(表2)。

3　考　　察

BMDと心血管系疾患については，低BMDや骨密度減少が，心血管疾患による死亡リスク上昇と関連するという報告や[3,4]，骨粗鬆症の閉経後女性は，年齢や心血管疾患の危険因子を考慮しても，心・血管系イベントの発生リスクが有意に高い[5]など，これまでに多方面からの研究が行われている。日本人を対象とした疫学研究においても，骨粗鬆症や動脈硬化の評価手法はそれぞれの研究で異なるが，BMDと動脈硬化の程度とのあいだに関連を認めたと報告されている[6～9]。本研究では，脳・心血管疾患の予知因子として有用とされるIMT[10]とBMDのデータを用いて，地域住民男女における両疾病間の関連について解析を行った。その結果，骨粗鬆症評価を腰椎BMDで行った場合，女性で動脈硬化のある者は，ない者に比べて骨粗鬆症有病の割合が高くなった。この結果は，これまでの先行研究と矛盾するものではなかった。

女性の骨粗鬆症と心血管疾患は，どちらも閉経後より罹患率が高くなることが臨床的に広く知られている。またエストロゲン受容体は，骨芽細胞や破骨細胞，血管内皮細胞，血管平滑筋細胞に存在することが確認されており，両疾患の進行に共通して関与する因子としてエストロゲンがあげられる。本研究において，女性で両疾病間に有意な関連が認められた要因の一つに，エストロゲンの関与が示唆される。

またエストロゲン以外にも，酸化脂質やビタミンD，副甲状腺ホルモン，オステオカルシン，オステオポンチン，ホモシステイン，アンジオテンシン，マトリックスグラプロテイン，オステオプロテジェリン，一酸化窒素，インターロイキン(IL-6)などは，骨と血管の相互に関与する共通因子として近年検証が進み，いわゆる「骨・血管相関」の機序が解明されつつある。

腰椎は大腿骨頸部に比べ，構成組織として海綿骨の占める割合が高い。エストロゲン減少による骨代謝への影響は，皮質骨よりも海綿骨のほうがより反映されやすいと考えられている。今回の結果において，腰椎と大腿骨に相違を認めた要因の一つとしてエストロゲンの関与が示唆される。

一方，変形性脊椎症では椎体に骨棘形成を認めるが，その割合は，特に男性において加齢に伴い高くなるため，BMDが高く判定されてしまう。また腹部の大動脈石灰化が存在する場合にも，腰椎BMDが過大評価される可能性があり，結果への影響は否定できない。

両疾患の進行には性ホルモン以外にも喫煙，糖尿病，高脂血症など共通の危険因子が存在する。今後，これらの交絡因子を考慮しての検討を要すると考える。

患者のQOL低下を招くおそれのある骨粗鬆症性骨折予防の観点から，動脈硬化の基盤となる高血圧や高脂血症など生活習慣病の日常診療において，骨粗鬆症についても評価や治療の必要性がある。また逆に閉経後女性の骨粗鬆症有病者の日常診療において，脳・心血管疾患発症の基盤となる動脈硬化の存在にも留意すること

が必要と考えられた。

ま と め

地域在住中高年者を対象に，骨粗鬆症と動脈硬化症の有病の関連について横断的解析を行った。女性では年齢とBMIで調整しても，腰椎BMDとIMTとのあいだに有意な関連を認め，骨粗鬆症と動脈硬化進展とのあいだに密接な関連が示唆された。

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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

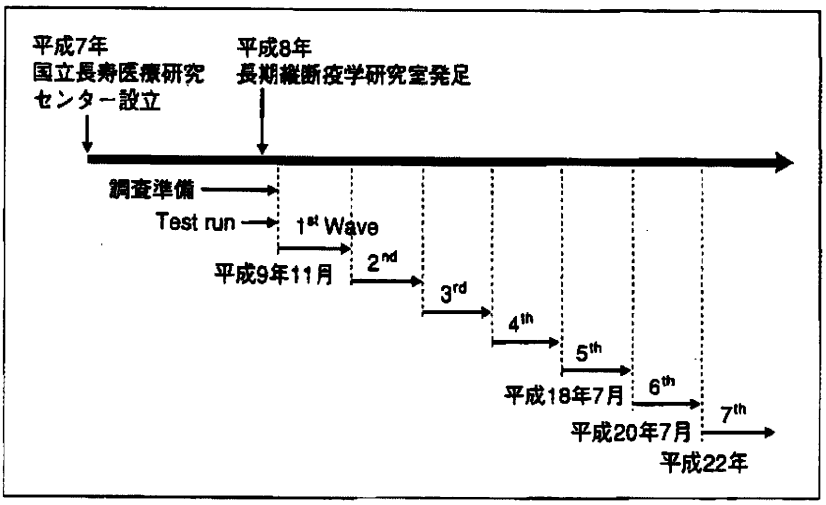

図 1　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の経緯
NILS-LSA では地域在住の中高年者約 2,400 人の 10 年以上にわたるデータが蓄積されている.

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].

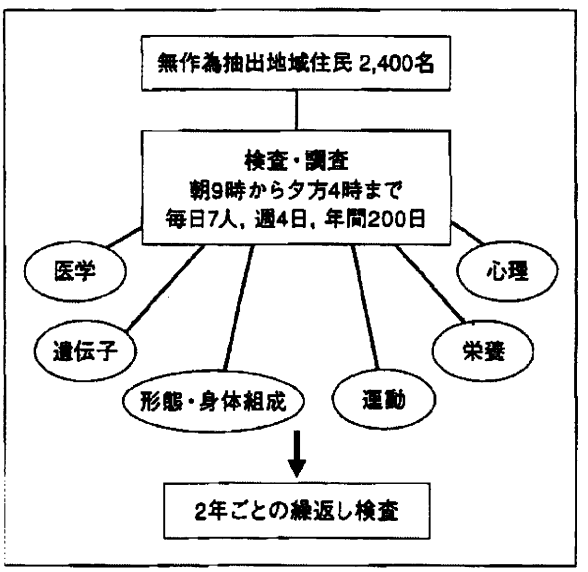

図 2　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の概要

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

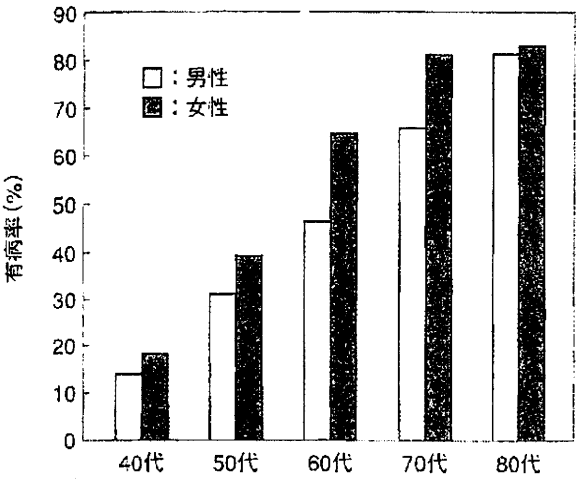

図 3　年代別，性別の膝変形性関節症の有病率
(Kellgren-Lawrence 分類 grade Ⅱ以上)

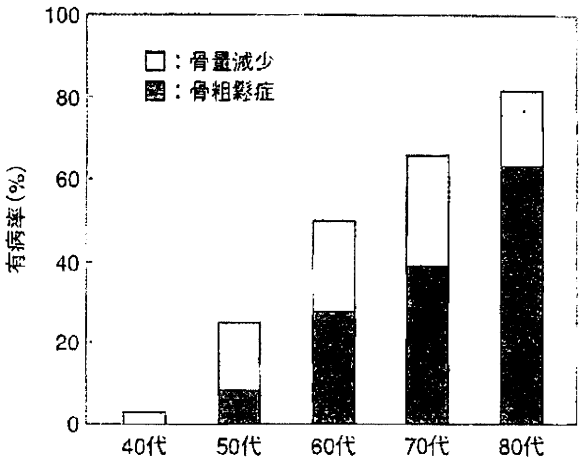

図 4　女性の年代別の骨粗鬆症および骨量減少の有病率(日本骨代謝学会診断基準による腰椎骨密度からの判定)

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