3.1 (95% CI 1.5–6.2)[46] and of pulmonary embolism was 4.5 (95% CI 1.1–19.5)[72] for raloxifene compared with placebo at 36 months. The estimated incidence of deep vein thrombosis in Japanese people is a tenth of that in Caucasian people (42 versus 370–420, respectively, per 1,000,000 people),[73] and the findings of this systematic review confirmed the low incidence of VTE in postmenopausal Japanese women taking raloxifene.[35,40] In addition, evidence from large-scale postmarketing surveillance studies showed that the incidence of stroke or fatal stroke was not different from the general female Japanese population after 1 year[41] or 3 years[75] of treatment with raloxifene. Although the blood–lipid profile of postmenopausal women taking raloxifene had improved (eg, decreases in both total cholesterol and LDL cholesterol),[21,33,35,36] there is no evidence that improved blood–lipid profiles are associated with better cardiovascular outcomes in postmenopausal women at increased risk of coronary heart disease.[75]

This systematic review retrieved only one publication reporting quality-of-life and pain findings in Japanese women. In this postmarketing surveillance study,[42] treatment with raloxifene improved health-related quality-of-life scores and relieved pain. This study is important, because prevalent vertebral fractures can be a major contributor to the health-related quality of life of postmenopausal women with osteoporosis. In particular, multiple vertebral fractures are of concern in Japan, as they are associated with chronic pain and incapacitating spinal deformities, deterioration in activities of daily living, and an increased risk of death.[9–14] Specifically, morphometric vertebral fracture in Japanese women is significantly associated with lower health-related quality-of-life scores,[76] and this loss of health-related quality of life occurred after incident vertebral fracture.[77] Further, in Japan, osteoporosis may also be a significant burden on the patient's family, who are responsible for providing caregiving support to elderly family members with osteoporosis.

There were several limitations with this systematic review. First, although the publications included in this review reported a broad range of findings for raloxifene (eg, BMD, bone turnover, lipid metabolism, and AEs), these findings were limited by the different methods used and the study quality (ie, there was only one placebo-controlled randomized trial and one randomized trial comparing raloxifene with a bisphosphonate). Second, few publications assessed raloxifene treatment for more than 1 year, despite the increased risks of VTE and stroke with long-term use of raloxifene.[75] Third, publications of raloxifene coadministered with active metabolites of vitamin D were included. However, excluding these studies is not clinically appropriate, because active vitamin D_3 analogs are widely prescribed in Japan concomitantly with antiresorptive agents to compensate for calcium absorption and inhibit subsequent parathyroid hormone secretion in osteoporosis patients. Fourth, we did not provide a separate analysis of those studies in which raloxifene was coadministered with active metabolites of vitamin D. Although active vitamin D_3 analogs are widely prescribed in Japan concomitantly with antiresorptive agents, only three[29,32,33] of the 15 publications included in this review assessed patients taking concomitant raloxifene and active vitamin D_3 analogs (alfacalcidol), and all included raloxifene monotherapy treatment groups. Last, although there were no restrictions on language and the bibliographies of retrieved systematic reviews were hand-searched to identify any publications not retrieved in the electronic search, other nonindexed publications and unpublished data were not included.

In conclusion, osteoporosis is a major health problem in the aging population of Japan and is underdiagnosed and undertreated.[78] If left untreated, fracture may occur, resulting in considerable pain and decreased health-related quality of life. Findings from this systematic review support the efficacy and effectiveness of raloxifene for preventing or reducing the risk of subsequent vertebral and/or nonvertebral fractures by improving BMD and reducing bone turnover in postmenopausal Japanese women with osteoporosis or osteopenia. Other findings suggest that raloxifene is well tolerated and can improve quality of life. However, these findings should be considered in light of the limitations of the publications and the risk–benefit profile of raloxifene.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of knee-extension strength with instrumental activities of daily living in community-dwelling older adults

Narumi Kojima,[1] Hunkyung Kim,[1] Kyoko Saito,[1] Hideyo Yoshida,[1] Yuko Yoshida,[1] Hirohiko Hirano,[1] Shuichi Obuchi,[1] Hiroyuki Shimada[2] and Takao Suzuki[2]

[1]*Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Itabashi-ku, and* [2]*National Center for Geriatrics and Gerontology, Obu-shi, Japan*

Aim: The purpose of the present study was to investigate the relationship between knee-extension (KE) strength and instrumental activities of daily living (IADL), and to examine the risk of IADL disability in relation to KE strength in community-dwelling older adults.

Methods: The participants were 1235 community-dwelling older adults (261 men and 974 women) in Tokyo who underwent a comprehensive health survey in 2009. The health survey included measurement of KE strength and a questionnaire on the Tokyo Metropolitan Institute of Gerontology (TMIG)-IADL. Pearson product-moment correlation coefficients and partial correlation coefficients were calculated separately for each sex for four parameters representing quadriceps muscle strength and TMIG-IADL. Pearson's χ^2-test of independence and the Cochran–Armitage test of trend were also carried out to determine the relationship between KE strength and IADL disability.

Results: In women, all correlations between the quadriceps muscle strength parameters and the TMIG-IADL score were statistically significant ($P < 0.0005$). The significance persisted remained even after factors regarding cognition or depression were taken into consideration. Furthermore, the percentage of female participants with IADL disability was dependent on KE strength; there was an inverse trend between KE strength and the percentage of people with IADL disability. In men, no significant relationship was found between KE strength and IADL.

Conclusions: KE strength and IADL correlated positively, and the percentage of people with IADL disability decreased with increasing KE strength in women. **Geriatr Gerontol Int 2014; 14: 674–680.**

Keywords: activities of daily living, aged, knee, muscle strength, quadriceps muscle.

Introduction

The instrumental activities of daily living (IADL) are the activities often carried out by a person who is living independently in a community setting during the course of a normal day, such as managing money, shopping, telephone use, travel in the community, housekeeping, preparing meals and taking medications correctly.[1] Declines in the ability to carry out these activities might result in the need for long-term care. Therefore, the unprecedented rate of aging seen in Japan today necessitates the identification of measures to prevent the decline of IADL in the elderly.

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Correspondence: Mr Narumi Kojima M (Master of Education), 35-2 Sakae-cho, Itabashi-ku, Tokyo, 173-0015, Japan. Email: nkojima@tmig.or.jp

Several studies have reported that hand muscle strength is related to IADL. For example, a meta-analysis of community-dwelling older participants by Judge *et al.* showed that handgrip strength was negatively related to the total number of IADL requiring assistance from others.[2] Sallinen *et al.* reported that handgrip strength below 37 kg for men and 21 kg for women increased the likelihood of mobility limitations, which are directly related to IADL disability.[3] A 3-year follow-up study by Ishizaki *et al.* also pointed out that weak handgrip strength was a significant predictor of functional decline in IADL performance.[4]

As most IADL involve walking, leg muscle strength might also greatly affect the performance of IADL. However, an association between lower-limb muscle strength and IADL cannot be assumed, as one could, for example, substitute a wheelchair for walking, to carry out each activity included in the IADL.

A multivariate analysis carried out by Uchida *et al.* showed that poor performance on the knee-raising test correlated strongly with decreased IADL performance.[5] A study by Azegami *et al.* involving 47 elderly people investigated the effect of lower-extremity muscle strength on IADL status in two ways: knee-extension (KE) in a single-joint task and total leg extension (TLE) in a multijoint task.[6] The authors found that there was a significant difference in TLE strength between participants with total and only partial IADL independence, whereas no such difference was found for KE strength in a single joint.

In many studies, the strength of lower-limb muscles has often been represented by KE strength,[7–9] as this measurement of the isometric strength of the quadriceps muscles in the sitting position is well established. The purpose of the present study was to examine the relationship between KE strength and IADL performance in a local elderly population.

Methods

Participants

The data were taken from a health survey carried out by Tokyo Metropolitan Institute of Gerontology (TMIG) for community-dwelling older adults in the Itabashi ward of Tokyo in 2009. The participants in the 2009 survey consisted of 1235 people (261 men and 974 women). This group of participants included two cohorts (2002 and 2006 cohorts). All the men ($n = 261$) and 405 of the women participated in a health survey carried out in 2002 (2002 cohort). Follow-up surveys were carried out for this cohort four times, including the survey in 2009. The remaining 569 women first participated in the health survey carried out in 2006 (2006 cohort). Follow-up surveys for this cohort were carried out once in 2007 and once in 2009.

A total of 15 men and 47 women whose IADL or KE data were not available were excluded from the study; the present study analyzed data from 246 men (age range, 77–91 years) and 927 women (age range, 72–91 years) (Table 1). The TMIG ethics committee approved this study. All participants gave their written consent.

Measurement of KE strength

KE strength was measured isometrically using a handheld dynamometer (μTas F-1; ANIMA, Tokyo, Japan). The participants were seated on a custom-made chair with their feet hanging. Participants practiced isometric knee extension by pushing against the tester's hand. The dynamometer was then placed 5 cm above the top of the lateral malleolus, and the chair was adjusted to ensure that the participant's knees were flexed at 90°. Voluntary maximal isometric knee extension effort was exerted twice on the dominant leg. Participants received consistent verbal encouragement as reinforcement. The greater value of two trials was used for analysis. The distance from the lateral knee joint space to the lateral point of the height of the dynamometer pad (F-L distance in Table 1) was measured to convert KE strength into KE torque. Those who were diagnosed with a serious medical problem (e.g. systolic blood pressure over 180 mmHg, diastolic blood pressure over 110 mmHg, or heart attack or cerebral stroke in the past 6 months) were excluded from the test for safety reasons.

Evaluation of IADL performance

IADL performance was assessed using a five-item list from the TMIG Index of Competence for instrumental self-maintenance,[10] which was developed for elderly Japanese participants and has been widely used in Japanese communities. The list assessed the following five activities: (i) using public transportation; (ii) shopping for daily necessities; (iii) preparing meals; (iv) paying bills; and (v) handling a bank account (Table 2). The response to each item was either "yes" (able to accomplish, 1 point) or "no" (unable to accomplish, 0 points). The IADL score (TMIG-IADL hereafter) was calculated as the total number of points.

Evaluation of other parameters potentially related to KE strength and IADL performance

To identify parameters that were related to both KE strength and IADL, which might result in a spurious correlation between the two, data on several other parameters were collected. Bodyweight was measured as a part of the body fat measurement. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE), for which a higher score indicates better cognitive function.[11] Depression was assessed using the Mini-International Neuropsychiatric Interview (MINI);[12] those who gave a negative response to both of the first two questions were categorized as normal, and those who gave a positive response to either of these questions were categorized as depressed. A history of disease (hypertension, stroke, heart disease, diabetes mellitus, hyperlipidemia, osteoporosis, anemia, chronic kidney deficiency, asthma, chronic occlusive pulmonary disease [COPD], pneumonia, osteoarthritis of the hip, gonarthritis, or fracture occurring above the age of 60 years) and the use of drugs was assessed using yes/no questions. Family status was examined using one multiple-choice question, and the participants were categorized as "living alone" or "living with someone".

Data analysis

For quantitative variables, means and standard deviations were calculated. For qualitative variables assessed

Table 1 Basic participant characteristics

			Male (n = 246) Mean ± SD	Female (n = 927) Mean ± SD	Difference between sexes
Mean ± SD		Age (years)	82.2 ± 3.5	79.5 ± 4.2	‡
		Height (cm)	160.8 ± 5.8	147.8 ± 5.6	‡
		Weight (kg)	58.4 ± 8.6	48.8 ± 7.6	‡
		F-L Distance (cm)	27.1 ± 2.3	25.0 ± 2.0	‡
		KES (N)	292.4 ± 82.8	209.1 ± 58.5	‡
		TMIG-IADL	4.9 ± 0.4	4.9 ± 0.5	N.S.
		MMSE	27.7 ± 2.3	27.6 ± 2.3	N.S.
Percent Positive	History	Depression	4.9%	3.9%	N.S.
		Hypertension	58.1%	55.8%	N.S.
		Stroke	10.2%	6.6%	N.S.
		Heart disease	23.6%	22.0%	N.S.
		Diabetes mellitus	11.8%	8.5%	N.S.
		Hyperlipidemia	18.7%	36.1%	‡
		Osteoporosis	6.1%	34.1%	‡
		Anemia	2.8%	3.8%	N.S.
		CKD	2.0%	1.1%	N.S.
		Asthma	4.1%	3.2%	N.S.
		COPD	4.5%	1.5%	‡
		Pneumonia	11.0%	6.9%	†
		Osteoarthritis of hip	2.4%	4.0%	N.S.
		Gonarthritis	15.4%	28.0%	‡
		Fracture after 60 years	13.0%	23.5%	‡
	Drug use	Anti-inflammatory	6.5%	9.5%	N.S.
		Oral steroid	1.2%	1.3%	N.S.
		Anti-osteoporosis	4.9%	30.3%	‡
		Living alone	8.1%	37.2%	‡

†$P < 0.05$, ‡$P < 0.01$. CDK, chronic kidney deficiency; COPD, chronic occlusive pulmonary disease; F-L Distance, distance from fulcrum to the point of load in knee extension task; KES, knee extension strength; SD, standard deviation.

Table 2 English translation of the questions constituting the Tokyo Metropolitan Institute of Gerontology instrumental activities of daily living

Question	Answer
1. Can you use public transportation (bus or train) by yourself?	Yes/No
2. Are you able to shop for daily necessities?	Yes/No
3. Are you able to prepare meals by yourself?	Yes/No
4. Are you able to pay bills?	Yes/No
5. Can you handle your own banking?	Yes/No

by yes/no questions, the percentage of positive responses was calculated. Differences between sexes were analyzed using the t-test or the χ^2-test.

We carried out a preliminary analysis to determine potentially confounding factors for the relationship between KE strength and IADL; correlations between parameters, such as body weight, MMSE, MINI, medical conditions and diseases, medication use, family status, and KE strength or TMIG-IADL, were examined individually. The statistical significance of Pearson's or Spearman's correlation coefficients was tested.

Pearson's correlation coefficients between four parameters representing quadriceps muscle strength (KE strength, KE torque, bodyweight-adjusted KE strength and bodyweight-adjusted KE torque) and TMIG-IADL scores were examined. Partial correlation coefficients using MMSE and MINI as the controlling variables were also calculated. The statistical significance of the correlations was tested.

The participants were classified according to quintiles of KE strength into five categories, and were also classified into two categories according to the presence of IADL disability; participants with a TMIG-IADL score of 1–4 were defined as having IADL disability.[13,14] The χ^2-test was carried out to determine the relationship

between the percentage of participants with IADL disability and KE strength. Cochran–Armitage tests of trend were carried out to determine whether there were any trends in the prevalence of IADL disability according to the KE strength.

As the distribution of TMIG-IADL was very skewed (just 2% of men and 3% of women scored ≤3 points), the analyses were also applied to a subgroup of participants whose TMIG-IADL score was between 4 and 5. All of these analyses were carried out using PASW Statistics 18 (IBM Japan, Tokyo, Japan), except for Cochran–Armitage tests, which were carried out using an Excel program (Microsoft, Redmond, WA, USA). The level of significance was set at $P < 0.05$.

Results

Participant characteristics

The age, height, weight, F-L distance and KE strength were greater in men than in women. Hyperlipidemia, osteoporosis, gonarthritis, fracture after 60 years-of-age, use of anti-osteoporosis drugs and living alone were higher in women than in men. COPD and pneumonia were higher in men than in women. (Table 1).

Preliminary analysis of individual correlations

In men, statistically significant correlations with KE strength were observed for bodyweight ($r = 0.346$; $P < 0.0005$) and the MMSE score ($r = 0.230$; $P < 0.0005$). Statistically significant correlations with the TMIG-IADL score were observed for the MINI ($\rho = -0.134$; $P = 0.035$), stroke ($\rho = -0.145$; $P = 0.023$), heart disease ($\rho = -0.138$; $P = 0.030$) and asthma ($\rho = -0.159$; $P = 0.012$). No parameters correlated with both KE strength and the TMIG-IADL score.

In women, statistically significant correlations with KE strength were observed for bodyweight ($r = 0.343$; $P < 0.0005$), MMSE ($r = 0.160$; $P < 0.0005$), MINI ($r = -0.089$; $P = 0.007$), heart disease ($r = -0.105$; $P = 0.001$), osteoporosis ($r = -0.111$; $P = 0.001$), anemia ($r = -0.087$; $P = 0.008$) and the use of anti-osteoporosis drugs ($r = -0.084$; $P = 0.010$). Statistically significant correlations with the TMIG-IADL score were observed for the MMSE ($r = 0.302$; $P < 0.0005$), MINI ($\rho = -0.208$; $P < 0.0005$) and stroke ($\rho = -0.097$; $P = 0.003$). Thus, the MMSE and MINI correlated with both KE strength and the TMIG-IADL score. We therefore took these two parameters into consideration when we carried out the partial correlation analysis.

Correlation analysis

In men, all correlations between quadriceps muscle strength parameters and the TMIG-IADL score were statistically non-significant (Table 3). In women, all the correlations were weak (R 0.157–0.173), but statistically significant ($P < 0.0005$) (Table 3). These correlations remained significant for women even when the analysis

Table 3 Correlation coefficients between parameters related to quadriceps muscle strength and Tokyo Metropolitan Institute of Gerontology instrumental activities of daily living score

	Sex	Parameter	Correlation coefficient	Statistical significance
All participants	Male ($n = 246$)	KES	0.022	N.S.
		KET	0.030	N.S.
		WA-KES	0.066	N.S.
		WA-KET	0.072	N.S.
	Female ($n = 927$)	KES	0.173	‡
		KET	0.173	‡
		WA-KES	0.157	‡
		WA-KET	0.166	‡
Subgroup of TMIG-IADL ≥ 4	Male ($n = 241$)	KES	−0.005	N.S.
		KET	−0.001	N.S.
		WA-KES	0.010	N.S.
		WA-KET	0.012	N.S.
	Female ($n = 899$)	KES	0.109	‡
		KET	0.100	‡
		WA-KES	0.133	‡
		WA-KET	0.128	‡

†$P < 0.05$, ‡$P < 0.01$. KES, knee extension strength; KET, knee extension torque; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology instrumental activities of daily living; WA-KES, weight-adjusted knee extension strength; WA-KET, weight-adjusted knee extension torque.

Table 4 Partial correlation coefficients, with Mini-Mental State examination and depression as the control variable, between parameters related to quadriceps muscle strength and Tokyo Metropolitan Institute of Gerontology instrumental activities of daily living score

	Sex	Parameter	Partial correlation coefficient	Statistical significance
All participants	Male (n = 234)	KES	0.009	NS
		KET	0.018	NS
		WA-KES	0.066	NS
		WA-KET	0.071	NS
	Female (n = 913)	KES	0.091	‡
		KET	0.091	‡
		WA-KES	0.085	†
		WA-KET	0.090	‡
Subgroup of TMIG-IADL ≥ 4	Male (n = 229)	KES	−0.017	NS
		KET	−0.011	NS
		WA-KES	0.014	NS
		WA-KET	0.017	NS
	Female (n = 879)	KES	0.088	‡
		KET	0.078	†
		WA-KES	0.115	‡
		WA-KET	0.108	‡

†$P < 0.05$, ‡$P < 0.01$. KES, knee extension strength; KET, knee extension torque; WA-KES, weight-adjusted knee extension strength; WA-KET, weight-adjusted knee extension torque.

included only those with TMIG-IADL scores of 4–5 (R 0.100–0.133; $P < 0.005$) (Table 3).

Using the MMSE and MINI as the controlling variables, all the partial correlations between the quadriceps muscle strength parameters and the TMIG-IADL score in men were statistically non-significant (Table 4). In women, all the partial correlations were weak (R 0.085–0.091), but statistically significant ($P < 0.05$; Table 4). These partial correlations for women remained significant even when analysis included only those with TMIG-IADL scores of 4–5 (R 0.078–0.115; $P < 0.05$) (Table 4).

Analysis of the ratio of IADL disability to KE strength

Male participants were classified by KE strength quintiles into the following five categories: very low, KE strength <229 N; low, KE strength 229–267 N; normal, 267–311 N; high, 311–355 N; and very high, KE strength >355N. The χ^2-test showed that IADL disability was independent of KE strength (Pearson's χ^2, 5.199; df, 4; $P = 0.267$) in men. The occurrence of IADL disability showed no trend related to KE strength (Cochran–Armitage test, $P = 0.828$) (Fig. 1). These results were also true for the subgroup of men whose TMIG-IADL scores were between 4 and 5.

Female participants were classified by KE strength quintiles into the following five categories: very low, KE strength <159 N; low, KE strength 159–192 N; normal, KE strength 192–221 N; high, KE strength 221–254 N; and very high, KE strength >254 N. IADL disability was dependent of KE strength (Pearson's χ^2, 23.685; df, 4; $P < 0.0005$). The occurrence of IADL disability decreased as KE strength increased; the percentage of participants with IADL disability was 12.9%, 6.5%, 6.3%, 4.3% and 1.1% for the grades very low, low, normal, high, and very high, respectively (Fig. 1), and this inverse trend was statistically significant (Cochran–Armitage test, $P < 0.0005$). These results were also true for the subgroup with TMIG-IADL scores between 4 and 5 (Pearson's χ^2, 11.811; df, 4; $P = 0.019$; Cochran–Armitage test, $P = 0.019$).

Discussion

The present study examined the relationship between KE strength and IADL in older adults living in a local area of Tokyo. In contrast to the study by Azegami *et al.*, the present results suggest that single-joint–task KE strength is significantly related to IADL in women.[6] In women, every KE strength parameter correlated with IADL. As partial correlations adjusted by cognitive function and depressive scale were also present, it is suggested that KE strength affects IADL independently. In women, KE strength was related to the prevalence of IADL disability. In men, no correlation between KE strength and IADL was observed. These results were the

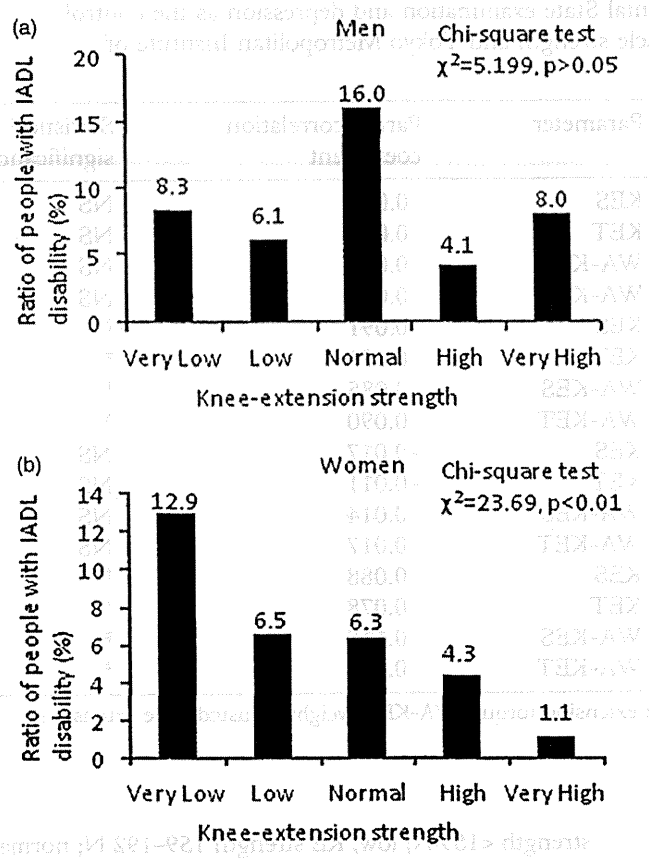

Figure 1 Prevalence of in instrumental activities of daily living (IADL) disability in relation to knee-extension strength (KES) in (a) men and (b) women. KES, men: very low, <229 N; low, 229–267 N; normal, 267–311 N; high, 311–355 N; very high, >355 N. KES, women: very low, <159 N; low, 159–192 N; normal, 192–221 N; high, 221–254 N; very high, >254 N. IADL, instrumental activities of daily living; KES, knee-extension strength.

same even when the subject population was limited to those who had relatively high TMIG-IADL scores (≥4).

Basic ADL has been reported to be affected by the knee extension strength; participants whose strength test scores were in the lowest tertile had two- to threefold the risk of ADL dependence than those in the highest tertile.[15] Therefore, the present result for men, suggesting no relationship between KE strength and the degree of IADL disability, seems counterintuitive.

To determine whether any one question specifically affected the sex-based differences, we carried out Pearson's χ^2-tests to assess the relationship between KE strength and the answer to each specific question (Q1–Q5). This result showed that, in women, the KE strength and answers to specific questions were related for all items except Q3, with a same trend as total IADL. In men, KE strength and the responses to every specific question were independent. This result suggests that the sex-based difference was not due to any particular item.

One possible explanation for the lack of such a relationship in men is that men had a generally higher KE strength than women. The muscular strength threshold required to carry out IADL independently is 2.8 N/kg (force divided by bodyweight) in the Japanese elderly population.[16] A total of 95% of our male and 92% of female participants had a KE strength above this threshold. This suggests that based on KE strength, more men were able to carry out IADL independently than women. This factor could partly explain the lack of correlation in men.

Another possible explanation for the lack of a correlation between KE strength and IADL performance in men is that cognitive function might have contributed more to IADL performance in men than in women. IADL were reported to be associated with memory and executive functioning in patients with mild Alzheimer's disease.[17] The absence of a relationship between KE strength and IADL performance in men could be partly explained if one argued that cognitive function played a greater role in men, especially because the men were older than the women. As aforementioned, however, the MMSE was related to IADL in women only. The average MMSE score was not different between men and women. Thus, it seems unlikely that cognitive function played a greater role in men than in women in determining IADL performance.

Another possible explanation is that effects of diseases were overshadowing the effect of KE strength. IADL was associated with a history of stroke, heart disease and asthma in men, but only with stroke in women. It is conceivable that IADL in men was more affected by medical conditions than women. Conceptual tradition in Japan regarding family roles might result in the maintenance of IADL irrespective of diseases. According to an international social survey, 77.7% of Japanese married people stated that grocery shopping was usually done by the woman within a couple, compared with 34–57% in six other developed countries.[18] The same trend follows for doing laundry and preparing meals.[18] Our data also show that 37.2% of the women were living alone compared with 8.1% of the men. High dependency on the woman for household jobs and the high percentage of women living alone suggest that women were carrying out many daily physical activities, which might have prevented the deterioration of IADL in response to disease.

Relative dominance by women of household jobs could also suggest a limitation of using TMIG-IADL to evaluate the IADL, especially in Japanese men. At least two questions in TMIG-IADL (Table 2) are closely related to jobs mainly carried out by women in Japan. We might need an improved index of IADL that is more sensitive in healthier men.

The present study showed that in women, KE strength correlated positively with IADL score, and the

degree of IADL disability decreased with increasing KE strength. This correlation was not observed in men. We might need to study a frail population to identify a correlation in men. We conclude that elderly women need to take measures to prevent lower-limb muscles from declining to maintain IADL.

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Disclosure statement

No potential conflicts of interest were disclosed.

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ORIGINAL ARTICLE

Usefulness of urinary CTX-II and NTX-I in evaluating radiological knee osteoarthritis : the Matsudai knee osteoarthritis survey

Nobuchika Tanishi · Hiroshi Yamagiwa · Tadashi Hayami · Hisashi Mera · Yoshio Koga · Go Omori · Naoto Endo

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Abstract
Background To assess the usefulness of the urinary crosslinked C-telopeptide of type II collagen (uCTX-II) or crosslinked N-telopeptide of type I collagen (uNTX-I) for evaluating radiological knee osteoarthritis (OA), a cross-sectional study was conducted in the cohorts of the Matsudai knee osteoarthritis survey performed in Niigata, Japan.
Methods Urine specimens and standing knee AP X-rays were obtained from 1040 subjects who provided informed consent. The relationship between these markers and gender, age (patients aged 40–59 or 60–79 years), use of bisphosphonates, and OA grades (K–L classification) were analyzed. The diagnostic ability of uCTX-II to detect radiological knee OA was confirmed in the over 60-year-old subjects using a ROC curve.
Results The over 60-year-old men with OA grade 3,4 group had significantly higher uCTX-II levels than the other OA grade groups. In the over 60-year-old women, the uCTX-II levels significantly increased according to the progression of the knee OA grade. No significant difference was observed between the uNTX-I levels in the different OA grade groups. From the standpoint of biomarkers, the higher quartiles of the uCTX-II and uNTX-I levels gradually included higher numbers of grade ≥2 OA subjects in the over 60 year-old women. The area under the curve (AUC) in ROC analysis of uCTX-II exhibited a significant association with the diagnosis of knee OA in women (AUC 0.63), although the accuracy was evaluated to be low in the single measurement of our health checkup-based analysis.
Conclusions This population-based study indicates that the uCTX-II level is strongly correlated with the knee OA grade in women over age 60. A further analysis is needed to clarify its predictive accuracy.

N. Tanishi · H. Yamagiwa (✉) · H. Mera · N. Endo
Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan
e-mail: hymgw@med.niigata-u.ac.jp

N. Tanishi
Department of Orthopedic Surgery, Niigata Rosai Hospital, 1-7-12 Touun-chou, Joetsu, Niigata 942-8502, Japan

T. Hayami
Department of Orthopedic Surgery, Saiseikai Niigata Daini Hospital, 280-7 Teraji, Nishi-ku, Niigata 950-1104, Japan

Y. Koga
Department of Orthopedic Surgery, Niigata Medical Center Hospital, 3-27-11 Kobari, Nishi-ku, Niigata 950-2022, Japan

G. Omori
Center for Transdisciplinary Research, Niigata University, 8050 Ikarashi 2-no-cho, Nishi-ku, Niigata 950-2181, Japan

Introduction

Knee osteoarthritis (OA) is becoming a common disease, because the average age of people in Japan has been increasing rapidly. Currently, the diagnosis of knee OA is based on symptoms, history, physical findings, laboratory data from the blood and synovial fluid and image assessments (e.g., X-ray, MRI). An evaluation of the function and pain in knee OA is performed based on the functional scores (e.g., Japanese Orthopaedic Association Knee OA score), and QOL assessments (e.g., WOMAC score). The findings of each examination and assessment are

considered to provide information about the current condition of the knee OA, and, therefore, to help determine the optimal treatment method at that point. These findings, however, are insufficient for evaluating the disease activity and predicting the prognosis of knee OA. Recently, OA biomarkers have been gathering attention as objective indices for providing an early diagnosis of knee OA and predicting the degree of progression. If useful joint biomarkers are found and can be applied clinically, they would be beneficial in terms of both the patient benefit and medical economics. Currently, the joint biomarkers being examined include substrate markers formed by degradation products of bone and joint tissues, enzymes that exist in the joints, inflammatory cytokines, etc. [1].

When type II collagen, which is the main component of joint cartilage, is degraded by a cartilage-degrading enzyme, a C-terminal crosslinking telopeptide of collagen type II (CTX-II) is produced and excreted in the urine. Garnero et al. [2, 3] have reported that the urinary CTX-II (uCTX-II) level was significantly elevated in patients with early rheumatoid arthritis, and that it could be used as a diagnostic index, predicting X-ray progression, and for evaluating the effects of drug therapy. In addition, patients with hip OA exhibited higher levels of uCTX-II than healthy subjects, and cases of rapidly developing hip OA had significantly higher uCTX-II levels than cases of slowly developing hip OA [4]. Moreover, the uCTX-II levels of patients with advanced radiological knee OA were higher [5, 6], thus, indicating the possibility that uCTX-II can be used as a joint biomarker.

There have been several reports regarding uCTX-II, but there are few reports of uCTX-II being used for Japanese patients with knee OA. In addition, regarding the correlation between knee OA and osteoporosis, although both conditions are common among women and share similar ages of onset, definite information has not yet been obtained about the potential utility of bone resorption biomarkers in OA. It has been experimentally revealed that subchondral bone resorption and subsequent bone sclerosis occurs in conjunction with the progression of knee OA [7]. The nature of the changes that occur to bone resorption markers in conjunction with the progression of knee OA is of great interest.

We have conducted a total of five epidemiological surveys on knee OA every 7 years from 1979 (1st survey) to 2007 (5th) in a rural area of Japan, during which time, resident health checkups were conducted every year. We have published reports regarding the risk factors for knee OA based on the findings of these surveys [8, 9]. To provide the initial step in verifying our hypothesis that uCTX-II can be used as a joint biomarker for knee OA, we reported the correlation between the knee OA X-ray grades of 296 subjects and the uCTX-II levels, as well as the levels of urinary N-terminal crosslinking telopeptide of type I collagen (uNTX-I), which is a biomarker of bone metabolism, while taking the age and gender of the subjects into consideration [10]. In this paper, in order to assess the potential utility of these biomarkers, we investigated the correlation between the knee OA X-ray grades of 1040 subjects and their uCTX-II and uNTX-I levels in the Matsudai cohort, taking the age, gender, menopausal status, and oral bisphosphonate treatment of the subjects into consideration.

Subjects and methods

During the 2007 annual comprehensive health check-up conducted in the Matsudai district (formerly Matsudai-machi), Tokamachi City, Niigata Prefecture, Japan, we collected urine specimens and took standing AP X-rays of the knees for approximately 1200 subjects from whom informed consent was obtained. The menopausal status and use of oral bisphosphonates were checked. The history of fractures within the past year was also ascertained, and those with fractures were excluded from the present analysis. The X-ray assessments were conducted blindly by the two senior authors (G. O. and Y. K.) in accordance with the Kellgren–Lawrence classification (G 0–4). Whenever there was a difference in grade between the right and left knees, the higher grade was included in the analysis. The subjects with total knee arthroplasty or unclassified knee OA grade were excluded. As with the past reports, patients with grades 0 and 1 were defined as the "non-OA" group, and those with grade 2 or higher were defined as the "OA" group. The casual urine specimens were collected from the participants and stored at −80 °C. The time of collection ranged from 9 a.m. to 2 p.m. The level of uCTX-II was measured using a Urine CartiLaps enzyme immunoassay kit (Immunodiagnostic Systems Limited, Tyne & Wear, UK), and that of uNTX-I was measured using an Osteomark NTx ELISA kit (Inverness Medical Innovations, Princeton, NJ, USA). The measured levels were corrected by the urine creatinine concentration (uCTX-II: ng/mmol Cr, uNTX-I: nmol BCE/mmol Cr). Outliers for uCTX-II and uNTX-I were defined as patients with values >1000 and >100, respectively, and were excluded from the analysis. A total of 1040 subjects (435 men and 605 women) ranging in age from 40 to 79 years were finally included in the following analyses. The numbers of the subjects, mean age, and mean body mass index according to gender and OA grade were as follows: 297 subjects (65.3 ± 9.7 years old, 22.6 ± 2.9 kg/m^2) in male OA G0,1, 106 subjects (72.3 ± 5.3, 23.3 ± 2.9) in male OA G2, 26 subjects (72.5 ± 4.9, 24.3 ± 3.3) in male OA G3, six subjects (74.7 ± 3.2, 23.1 ± 3.6) in male OA G4, 319

subjects (60.7 ± 9.5, 22.0 ± 3.0) in female OA G0,1, 183 subjects (70.3 ± 6.0, 22.8 ± 2.7) in female OA G2, 71 subjects (71.6 ± 6.1, 24.6 ± 3.2) in female OA G3 and 32 subjects (72.9 ± 5.1, 24.9 ± 4.1) in female OA G4. The age and BMI gradually increased according to the severity of OA, as shown in the previous study [8], with the exception of BMI in of men with OA G4.

The relationships between age, oral bisphosphonates, radiological knee OA grades, and values of biomarkers (uCTX-II and uNTX-I) were analyzed. In addition, the subjects were divided into four quartiles using the values of two biomarkers, and the distribution of the OA grades in each quartile was analyzed. In order to investigate the diagnostic ability of uCTX-II to detect OA knee (grade ≥2), receiver operator characteristic (ROC) curves were employed to display the sensitivity, specificity and area under the curve (AUC) in the over 60-year-old subjects.

For the statistical analysis, the Mann–Whitney *U* test, Kruskal–Wallis *H* test, and Chi square test, and ROC curve were used, and a value of $p < 0.05$ was defined to be statistically significant. The Prism 6 software program (GraphPad Software, Inc., La Jolla, CA, USA) was used to perform the analysis. Values are shown as the median. The study protocol was approved by the Ethics Committee of Niigata University Graduate School of Medical and Dental Sciences.

Results

Comparison of the levels of uCTX-II and uNTX-I by age in the non-OA group

Both biomarkers were compared between the non-OA (G0,1) 40-year-old to 59-year-old and 60-year-old to 79-year-old groups to eliminate the effects of knee OA. Forty-year-old to 59-year-old women were further divided by their menopausal status.

In men, the median uCTX-II levels in the 40-year-old to 59-year-old and 60-year-old to 79-year-old groups were 180.2 and 170.5 ng/mmol Cr, respectively (not significantly different). In women, the median uCTX-II level in the pre-menopausal 40-year-old to 59-year-old, post-menopausal 40-year-old to 59-year-old, and 60-year-old to 79-year-old groups were 71.8, 153.3 and 156.4 ng/mmol Cr, respectively. The uCTX-II levels in the post-menopausal 40-year-old to 59-year-old group and the 60-year-old to 79-year-old group were significantly higher than those in the pre-menopausal 40-year-old to 59-year-old group (Fig. 1a).

The median uNTX-I levels in the 40-year-old to 59-year-old and 60-year-old to 79-year-old men with grade 0 and 1 OA were 30.2 and 33.1 nmol BCE/mmol Cr, respectively (not significantly different). The median uNTX-I levels in the pre-menopausal 40-year-old to 59-year-old, post-menopausal 40-year-old to 59-year-old, and 60-year-old to 79-year-old women with grades 0 and 1 OA were 32.4, 44.0 and 40.6 nmol BCE/mmol Cr, respectively. The uNTX-I levels in the post-menopausal 40-year-old to 59-year-old group and the 60-year-old to 79-year-old group were significantly higher than those in the pre-menopausal 40-year-old to 59-year-old group (Fig. 1b).

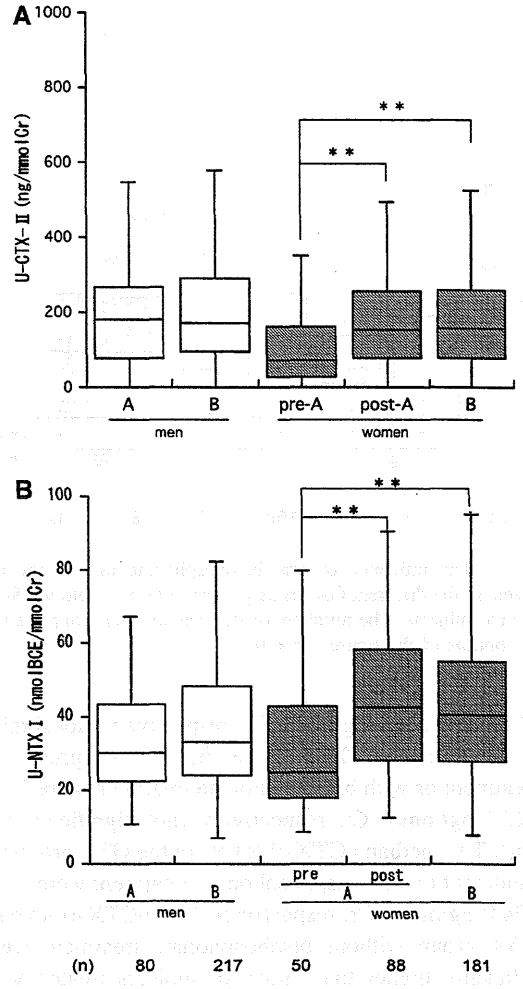

Fig. 1 The relationship between the age and uCTX-II level in the non-OA group (knee X-ray OA grade 0 and 1) subjects. **a** Subjects aged 40–59 years, **b** 60–79 years. *pre* pre-menopausal, *post* post-menopausal. The numbers of subjects are shown at the *bottom* **b**. Each *box* represents the 25th/50th (median) to 75th percentiles. The *lines* outside the *box* represent the 10th and 90th percentiles. $^{**}p < 0.01$

Influence of bisphosphonates on the uCTX-II levels

The uCTX-II levels were compared in the G0,1, G2, and G3,4 groups of 60-year-old to 79-year-old women with and without a history of oral bisphosphonate treatment (Fig. 2). The median uCTX-II levels in the G0,1 group in subjects that were untreated or treated with bisphosphonates were

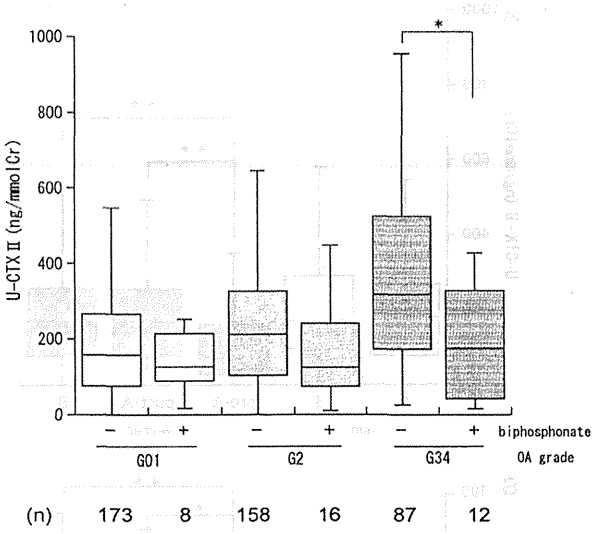

Fig. 2 The influence of oral bisphosphonate use on the uCTX-II levels in the different OA grade groups of 60-year-old to 79-year-old female subjects. The numbers of subjects in each group are shown at the *bottom* of the figure. $*p < 0.05$

157.7 and 127.0 ng/mmol Cr, respectively (not significant). The median uCTX-II levels in the G2 group without treatment or with bisphosphonate treatment were 212.0 and 125.5 ng/mmol Cr, respectively (not significantly different). The median uCTX-II levels in the G3,4 group without treatment or with bisphosphonate treatment were 317.4 and 174.8 ng/mmol Cr, respectively. The uCTX-II levels in the G3,4 group without bisphosphonate treatment were significantly higher than those in subjects treated with bisphosphonates. Thus, subjects with oral bisphosphonate treatment were eliminated from subsequent analyses.

Comparison of the uCTX-II levels based on the X-ray OA grade

In the 40-year-old to 59-year-old men, the median uCTX-II levels in the G0,1 and G2 groups were 180.2 and 137.5 ng/mmol Cr, respectively (not significantly different). There were no cases of G3,4 OA in this age group (Fig. 3).

In the 60-year-old to 79-year-old men, the median uCTX-II levels were 170.5 ng/mmol Cr in the G0,1 group, 152.7 in the G2 group, and 253.0 in the G3,4 group. The G3,4 group had significantly higher uCTX-II levels than the other groups. The mean age of each group with regard to the OA grade was not significantly different (70.2 ± 5.2, 72.8 ± 4.2, and 72.9 ± 4.7 in the G0,1, G2, and G3,4 groups, respectively).

In the pre-menopausal 40-year-old to 59-year-old women, the median uCTX-II levels were 71.8 ng/mmol Cr in the G0,1 group and 149.5 in the G2 group. There were no cases of G3,4 OA. A statistical analysis of this group was not performed because of the small number of subjects.

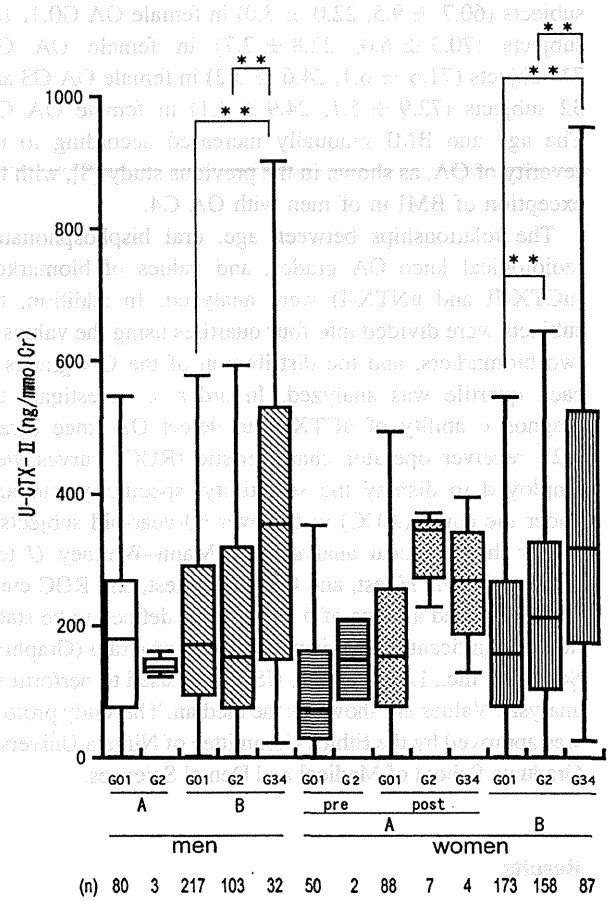

Fig. 3 The relationship between the knee X-ray OA grade and uCTX- II level. **a** Subjects aged 40–59 years, **b** 60–79 years. *pre* pre-menopausal, *post* post-menopausal. The numbers of subjects are shown at the *bottom* of the *panels*. A statistical analysis was performed to examine the differences between the OA grade groups for each age group. $**p < 0.01$

In the post-menopausal 40-year-old to 59-year-old women, the median uCTX-II levels were 153.5 ng/mmol Cr in the G0,1 group, 344.6 in the G2 group and 267.3 in the G3,4 group. There were no significant differences between any of the groups.

In the 60-year-old to 79-year-old women, the median uCTX-II levels were 157.7 ng/mmol Cr in the G0,1 group, 212.0 in the G2 group and 317.6 in the G3,4 group. The G3,4 group had significantly higher uCTX-II levels than the other groups. The G2 group also had significantly higher uCTX-II levels than the G0,1 group. The age (mean ± SD) of each group based on the grade was not significantly different (68.0 ± 5.2, 71.2 ± 5.0, and 71.7 ± 5.0 in the G0,1, G2, and G3,4 groups, respectively).

To assess the potential of using uCTX-II as a biomarker, the 60-year-old to 79-year-old subjects were divided into quartiles based on the uCTX-II values, and the distribution of OA grades was compared (Fig. 4). An OA grade greater

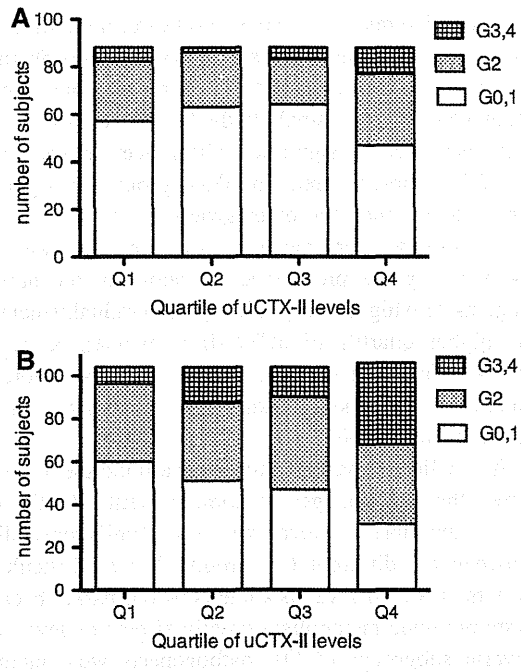

Fig. 4 There was an increased uCTX-II level and distribution of OA grades in 60–79 year-old **a** male ($n = 352$) and **b** female ($n = 418$) subjects. The mean values of uCTX-II (ng/mmol Cr) for each quartile from Q1–4 were 42.6, 130.3, 237.7, and 548.8 in males, and 49.4, 151.8, 262.6, and 532.3 in females. **a** n.s. and **b** $p < 0.0001$ according to the Chi-square test. The mean age of each group was not significantly different

than or equal to G2 gradually increased as the mean uCTX-II of the quartile increased in women (Fig. 4b), although men showed no clear trend (Fig. 4a).

Comparison of the uNTX-I levels based on the X-ray OA grade

Considering that the effects of age on the uNTX-I levels are small in men, 40-year-old to 79-year-old men were compared without dividing them by age. There were no significant differences in the uNTX-I levels according to OA severity between any of the groups in either gender (Table 1).

To examine the potential use of uNTX-I as a biomarker, 60-year-old to 79-year-old subjects were divided into quartiles based on their uNTX-I values, and the distribution of OA grades was compared (Fig. 5). The higher quartile of uNTX-I in women included significantly more subjects of radiological knee OA (G2 and G3,4) (Fig. 5b), while men showed no clear trend (Fig. 5a).

ROC analysis to examine the diagnostic ability of the uCTX-II level

Based on the results above, we examined the sensitivity and specificity for diagnosing OA (grade 0,1 or grade ≥2)

Table 1 Relationship between the grade of knee X-ray OA grade and the median levels of uNTX-I

Gender	Age range	uNTX-I (nmol BCE/mmol Cr)		
		OA G0,1	OA G2	OA G3,4
Men	40–79	31.9 (297)	32.4 (106)	33.0 (32)
Women	40–59 (pre)	24.9 (50)	40.7 (2)	Not available (0)
	40–59 (post)	42.6 (88)	41.7 (7)	27.9 (4)
	60–79	40.7 (173)	44.6 (158)	44.8 (87)

pre pre-menopausal, *post* post-menopausal, () numbers of subjects

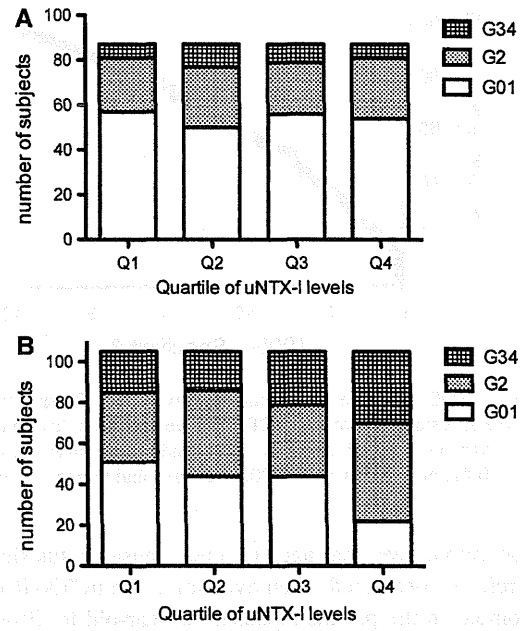

Fig. 5 The uNTX-I level and distribution of OA grades in 60–79 year-old **a** male and **b** female subjects. The mean values of uNTX-I (nmol BCE/mmol Cr) for each quartile from Q1–4 were 17.4, 28.0, 39.3, and 62.1 in males, and 20.7, 36.2, 50.5, and 75.4 in females. **a** n.s. and **b** $p = 0.0015$ according to the Chi square test. The mean age of each group was not significantly different

according to the in the level of uCTX-II and depicted the findings in ROC curves (Fig. 6). The AUC of the uCTX-II level to diagnose radiological knee OA indicated the better accuracy in women than in men; however, low accuracy was observed in the single measurement of the uCTX-II level in this annual health check-up.

Discussion

We first examined the changes in uCTX-II and uNTX-I based on age. In the non-OA subjects, these biomarker levels were significantly affected by age only in women, as had already been shown in the previous studies [11–13]. Our data

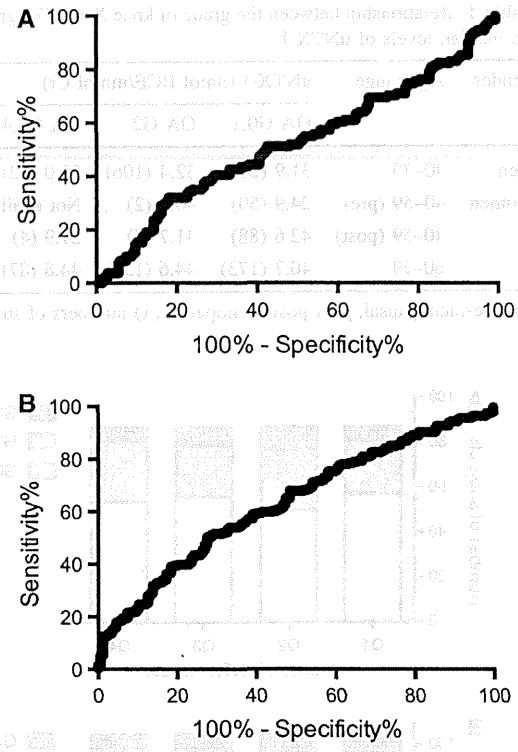

Fig. 6 ROC curve identifying the sensitivity and 100-specificity (%) of the measurement of the uCTX-II levels in men (**a**) and women (**b**) over 60 years of age. The area under the curve was 0.5229 ($p = 0.47$) and 0.6321 ($p < 0.0001$) in men and women, respectively

also emphasized that age and menopausal status should be carefully considered when evaluating the uCTX-II level in women. In the pre-menopausal 40-year-old to 59-year-old non-OA (G0,1) women, the uCTX-II level was 71.8 (median) ng/mmol Cr, the lowest value of the group in this study, which is quite reasonable. However, approximately 10 % of the subjects in this group showed elevation (e.g., >300 ng/mmolCr) of the uCTX-II values. This result raises the possibility that, in these subjects, radiological knee OA change may occur within a few years, or that OA changes in other joints, such as the lumbar spine, may already exist. A longitudinal follow-up study of knee X-ray changes is needed to clarify the usefulness of uCTX-II in this group.

The uCTX-II level decreases significantly in response to bisphosphonates [12]. This must be carefully considered when analyzing the OA biomarkers. In this study, the uCTX-II levels tended to be lower in subjects treated with bisphosphonates than in those without in all grade groups, and a significant difference was observed in the grade 3,4 group. Our data suggested that there was a 40–45 % reduction of the CTX-II values in the women OA groups (≥G2) resulting from the use of oral bisphosphonates.

In the 40-year-old to 59-year-old subjects of both genders, there were no significant differences in the uCTX-II values between different OA grades. However, no definitive conclusions could be made, because this age group only included the G0,1 and G2 groups, and the number of subjects in the G2 group was relatively small. In the 60-year-old to 79-year-old men, there were no significant differences between the G0,1 and G2 groups, whereas the G3,4 group had significantly higher levels than the other groups. In the 60-year-old to 79-year-old women, the uCTX-II levels increased as the X-ray OA grade progressed. In addition, the number of subjects with higher OA grades (≥G2) gradually increased in the higher quartile of uCTX-II in women, as shown in Fig. 4b. This data suggests that uCTX-II is a more useful diagnostic biomarker for knee OA in women than in men above the age of 60.

It is believed that bone turnover around the joints would affect the OA changes in some patients. In the current study, the uNTX-I level was not significantly different between the different OA groups. It was difficult to use only the uNTX-I level as a knee OA biomarker because (1) systemic bone metabolism greatly affects its level, and (2) several subgroups of OA pathogenesis were included in this population-based study. Interestingly, our data showed that approximately 80 % of subjects in the highest uNTX-I quartile of women had radiological knee OA changes (≥G2). This high level of bone resorption might have been derived from (1) low physical activity associated with severe knee pain due to OA, and (2) generalized OA changes, including knees with systemic bone resorption, or due to other causes. The weak but positive correlation between the levels of uCTX-II and uNTX-I in the 60–79 year-old women with knee OA of G3,4 in this study (data not shown), supports the above-mentioned assumptions. In order to demonstrate the effect of bone metabolism on knee OA changes, an evaluation of the local bone turnover around the knee would be necessary.

To evaluate the diagnostic ability of the uCTX-II level to detect radiological knee OA according to the "BIPED" criteria [14], a ROC analysis was performed. Our study showed that the uCTX-II levels in women are significantly associated with radiological knee OA; however, the diagnostic accuracy of a single measurement is low. As the onset and progression of OA occurs over a period of time, multiple measurements of biomarkers would provide better diagnostic ability. Sowers et al. [15] showed that five biennial measures of the CTX-II level obtained over a 10-year period were predictive of subsequent OA knee, although the sensitivity and specificity for changes over time in the CTX-II level to predict X-ray-defined OA knee using a ROC curve analysis were "modest". To confirm the usefulness of biomarkers as a diagnostic biomarker and predictor of knee OA occurrence and progression, we have already performed a prospective 6th survey at a 3-year interval (2010), and the data analysis is now ongoing.

There are a number of limitations associated with this study that should be considered when interpreting the results. Although uCTX-II and uNTX-I are systemic biomarkers, we only checked knee X-rays, because this study was population-based and conducted as part of regular health check-ups. An evaluation of other joints and the spine using X-rays was not performed. Significant diurnal variation in the biomarker expression has been reported [16]. Their study showed that the levels of uCTX-II were highest prior to arising from bed (T0) and 1 h arising from bed (T1) and decreased at 4 h (T2) after arising from bed and remained stable after 12 h (T3) of daily activity. Our health checkups were performed at various times from 9 a.m. to 2 p.m. We should consider the possibility that circadian variability affected our results although the timing of sample collection in our study was usually around their "T2", which was considered to be a relatively stable phase of diurnal variation in their study. Furthermore, a recent review suggested that the uCTX-II is not a specific marker of articular cartilage breakdown, but it reflects, to some extent, the remodeling of calcified cartilage [1]. However, in spite of these drawbacks, clear differences were demonstrated between the knee OA X-ray grades and uCTX-II levels in the cross-sectional observation. Although it is inevitable that population-based studies will include some unclear findings, the relatively large number of subjects make the present results representative of the general Japanese population.

In conclusion, this study provides invaluable information about the relationship between uCTX-II and the X-ray knee OA grade after adjusting for age, gender, menopausal status, and the use of bisphosphonates. The number of subjects included in this study was 3.5 times higher than that of our previous study [10]. This cross-sectional study indicates that uCTX-II is correlated with the radiological knee OA grade in subjects over 60 years of age, and it can be used as a method to evaluate OA, especially in females. We are now working on analyzing whether the occurrence and progression of knee OA can be predicted in this cohort of patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial

Muneaki Ishijima[1*], Toshitaka Nakamura[2], Katsuji Shimizu[3], Kunihiko Hayashi[4], Hiraku Kikuchi[5], Satoshi Soen[6], Go Omori[7], Toshihiko Yamashita[8], Yuji Uchio[9], Junji Chiba[10], Yuki Ideno[4], Mitsuaki Kubota[1], Hisashi Kurosawa[1], Kazuo Kaneko[1] and for the Research Group of Cartilage Metabolism

Abstract

Introduction: While many of the commonly used conservative treatments for knee osteoarthritis (OA) have been recognized to be effective, there is still insufficient evidence available. Among the pharmacological treatments for knee OA, oral non-steroidal anti-inflammatory drugs (NSAIDs) act rapidly and are recommended for the management of OA. However, frequent and serious adverse effects of NSAIDs have been recognized. Intra-articular injections of hyaluronic acid (IA-HA) for the treatment of knee OA have been shown to reduce pain and improve joint function. However, there has been no qualified direct comparison study of the efficacy and safety between IA-HA and NSAIDs for patients with knee OA. The aim of this study was to clarify the efficacy and safety of early-phase IA-HA in comparison to those of NSAIDs for patients with knee OA.

Methods: This multicenter, randomized, open-label, parallel-group, non-inferiority comparison study with an oral NSAID involved a total of 200 patients with knee OA. An independent, computer-generated randomization sequence was used to randomly assign patients in a 1:1 ratio to NSAIDs three times per day for five weeks (n = 100) or IA-HA once a week for five weeks (n = 100). The primary endpoint was the percentage change in the patient-oriented outcome measure for knee OA, the Japanese Knee Osteoarthritis Measure (JKOM) score. All patients were questioned regarding any adverse events during treatment. The full analysis set (FAS) was used for analysis. The margin of non-inferiority was 10%.

Results: The analyses of primary endpoint included 98 patients in the IA-HA group and 86 patients in the NSAID group. The difference in the percentage changes of the JKOM score between the two intervention arms (IA-HA; -34.7% ($P<0.001$), NSAID; -32.2% ($P<0.001$)) was −2.5% (95% confidence interval (CI): -14.0 to 9.1), indicating IA-HA was not inferior to NSAID. The frequency of both withdrawal and adverse events in the IA-HA group were significantly lower than those in the NSAID group ($P = 0.026$ and 0.004, respectively).

Conclusions: The early efficacy of IA-HA is suggested to be not inferior to that of NSAIDs, and that the safety of the early phase of IA-HA is superior to that of NSAIDs for patients with knee OA.

Trial registration: UMIN Clinical Trials Registry (UMIN-CTR), UMIN000001026.

* Correspondence: ishijima@juntendo.ac.jp
[1]Department of Medicine for Orthopaedics and Motor Organ, Juntendo University Graduate School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
Full list of author information is available at the end of the article