Table 2 Results of the primary endpoint of the study

		JKOM score			% change of JKOM score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
IA-HA (n = 98)	Pre-treatment	33.8	15.9	<0.001	−34.7	39.6	−2.5 (−14.0 to 9.1)
	Post-treatment	21.5	14.6				
NSAID (n = 86)	Pre-treatment	32.0	14.0	<0.001	−32.2	39.8	
	Post-treatment	22.0	15.5				

The effect of the treatment of either IA-HA or NSAID for the patients with knee OA evaluated by JKOM score (left) and percentage (%) change of JKOM score (right). A *P* value less than 0.05 was considered to be significant. JKOM, Japanese Knee Osteoarthritis Measure; IA, intra-articular; HA. hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

reduced by the treatment ($P<0.001$, Table 3). The percentage change from baseline in the VAS score in the NSAID group was −36.0%. The pain VAS in the IA-HA group was also significantly reduced by the treatment, with a percentage change from baseline in the VAS score of −41.2% ($P<0.001$). The difference in the percentage changes in the pain VAS score between the two intervention arms (secondary endpoint) was −5.2% (95% CI: -23.8 to 13.4%).

Subanalyses

When the patients were divided into two groups (responders or non-responders) by the OMERACT-OARSI response criteria [16], 69.7% (69/99) of the patients in IA-HA group were classified as 'responders', while 62.4% responders were found (58/93) in the NSAID group. Again, there were no significant differences in the frequency of 'responders' between these two groups ($P = 0.283$).

A multiple logistic regression analysis, which was adjusted for age, K/L grade, BMI and the participating medical centers, confirmed the lack of significant differences in the odds ratio of responders between those who received IA-HA treatment and those who received NSAID treatment (odds ratios: 1.47 (95% CI: 0.761 to 2.83)).

We further investigated whether IA-HA is broadly effective from very early (K/L grade of 1) to moderate stages of knee OA (K/L grade of 3) (Table 4). Both IA-HA and NSAID groups significantly reduced the patient-oriented outcome measure evaluated by the JKOM score in the patients with both a K/L grade of 2 and 3. In patients with a K/L grade of 1, IA-HA treatment also reduced the JKOM score, but this reduction was not significant ($P = 0.058$). On the other hand, NSAID treatment of this group significantly reduced the JKOM score ($P = 0.001$).

Safety analyses

During the five weeks of examination, nine of ninety-nine patients (9.1%) in the IA-HA group were withdrawn from the study (one patient's symptoms improved and eight patients were lost to follow-up). Nineteen of ninety-three patients (20.4%) of NSAID group were withdrawn from the study (five patients experienced side effects, four withdrew consent, two patient's symptoms improved, and eight were lost to follow-up). The frequency of the withdrawal rate in the IA-HA group was significantly lower than that in the NSAID group ($P = 0.026$, Table 5).

Serious adverse events, including gastrointestinal (GI) hospitalization, were not observed in both groups during this study. As one patient complained of stiffness in the affected knee after injection, the frequency of adverse events in patients treated with the IA-HA was 1.0%. Ten (symptom related to GI tract disorder, seven; drug allergy, three) of ninety-three patients (10.8%) exhibited adverse events in those treated with the NSAID. The frequency of adverse events in the IA-HA group was significantly lower than that of those in NSAID group ($P = 0.004$, Table 5).

Discussion

This short-term trial clearly demonstrated that both the IA-HA at weekly intervals and daily oral NSAID over five weeks significantly improved both the clinical symptoms evaluated by the patient-oriented outcome measure

Table 3 Results of the secondary endpoint of the study

		Pain VAS			% change of VAS score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
IA-HA (n = 97)	Pre-treatment	60.1	22.4	<0.001	−41.2	52.7	−5.2 (−23.8 to 13.4)
	Post-treatment	31.8	24.1				
NSAID (n = 85)	Pre-treatment	55.5	21.8	<0.001	−36.0	73.8	
	Post-treatment	31.9	23.9				

The effect of the treatment of either IA-HA or NSAID for the patients with knee OA evaluated by pain VAS score (left) and percentage (%) change of VAS score (right). A *P* value less than 0.05 was considered to be significant. VAS, visual analog scale; IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

Table 4 JKOM score and percentage change of JKOM score by K/L grade subgroup

		JKOM score			% change of JKOM score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
K/L grade 1							
IA-HA (n = 15)	Pre-treatment	24.8	13.0	0.058	−9.3	78.0	25.7 (−19.3 to 70.7)
	Post-treatment	18.7	12.6				
NSAID (n = 14)	Pre-treatment	35.9	15.4	0.001	−34.9	26.0	
	Post-treatment	23.4	15.7				
K/L grade 2							
IA-HA (n = 48)	Pre-treatment	33.1	14.7	<0.001	−43.8	27.1	−9.2 (−24.4 to 6.0)
	Post-treatment	18.8	12.6				
NSAID (n = 45)	Pre-treatment	30.8	13.9	<0.001	−34.6	44.9	
	Post-treatment	20.4	14.5				
K/L grade 3							
IA-HA (n = 35)	Pre-treatment	38.6	17.1	<0.001	−33.1	23.6	−6.2 (−21.6 to 9.3)
	Post-treatment	26.4	16.9				
NSAID (n = 27)	Pre-treatment	31.9	13.6	0.003	−26.9	37.0	
	Post-treatment	23.7	17.3				

A *P* value less than 0.05 was considered to be significant. JKOM, Japanese Knee Osteoarthritis Measure; IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug; K/L, Kellgren-Laurence grade.

and the pain severity evaluated by a VAS. No significant differences in the symptom-modifying effects were observed during this short period. In addition, the safety of the early phase of IA-HA treatment was superior to that of the NSAID in the patients with knee OA.

HA is a large glycosaminoglycan composed of repeating disaccharides of glucuronic acid and N-acetyl glucosamine that is naturally present in synovial fluid. Several protective properties of HA have been reported including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication [19]. Numerous clinical trials, meta-analyses and systematic reviews have indicated its clinical efficacy for knee OA [5,9,10,20]. Based on these previous findings, the OARSI recommendations that were revised in 2010 summarized the effect size (ES) of IA-HA at 0.60 (95% CI; 0.37, 0.83). However, as the ES declined to 0.22 (95% CI; -0.11, 0.54) when only the high-quality trials were selected [5], controversy remains regarding the efficacy of HA in treating knee OA [8]. A recent meta-analysis concluded that the pain reduction by IA-HA is observed later than that of intra-articular corticosteroids [9]. In addition, the effects of IA-HA for knee OA pain continued over six months post-intervention [10]. However, few studies have been conducted to clarify the early effects and safety of IA-HA in comparison to those of NSAIDs. The results of this study clearly indicated that the early efficacy of IA-HA was not inferior in comparison to that of the NSAID.

Table 5 Withdrawal and harmful events during the study

Withdrawn	Completed	Withdrawn	Frequency (%)	*P*
IA-HA (n = 99)	90	9	9.1	0.026
NSAID (n = 93)	74	19	20.4	
Harmful events	**Not occurred**	**Occurred**	**Frequency (%)**	***P***
IA-HA (n = 99)	98	1	1.0	0.004
NSAID (n = 93)	83	10	10.8	

IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

A number of HA products with a variety of the molecular weights, ranging from approximately 600 to 6,000 kDa, have been developed as IA-HA for the treatment of OA [8]. The considerable heterogeneity of outcomes between trials may be due in part to differences in HA products [5]. High-molecular-weight HA (>6,000 kDa) is suggested to have greater effects in comparison to lower-molecular-weight HA [8]. On the other hand, the intra-articular injection of high-molecular-weight HA (>6,000 kDa) showed a greater frequency of adverse events, such as pain flares, and hot and swollen knees, which typically occurred 24 to 72 hours after injection [21]. There were no cases of painful, hot or swollen knees during the study.

The molecular mechanisms underlying the efficacy of IA-HA for OA remain unclear. OA is frequently associated with the signs and symptoms of inflammation, including joint pain, swelling and stiffness leading to significant functional impairment and disability [2]. Synovitis plays an important role in inducing the pain, swelling and stiffness in OA [22], and the severity of synovitis is well correlated with the JKOM score of the patients with knee OA [23]. It has recently been reported that HA inhibits the activities of matrix

metalloproteinases and aggrecanases which are, at least in part, involved in OA cartilage degradation as a result of their induction by proinflammatory cytokines, such as interleukin (IL)-1 [19,24-26]. Therefore, HA is speculated to modify the structural damage of joints and the rate of OA progression in addition to the symptom-modifying effect [27], although further studies are required.

In this trial, the early efficacy of IA-HA was compared with that of NSAID for the treatment of knee OA. NSAIDs have also been proven to be an effective conservative treatment for knee OA [5]. However, a high incidence of serious GI tract adverse events associated with the use of oral NSAIDs was also demonstrated in a population-based cohort study of older patients [28]. In addition, the hospitalization due to GI tract side effects in patients receiving non-selective NSAIDs was twice as high as that in those given the cyclooxygenase (Cox)-2 selective agent, celecoxib, or a non-selective NSAID together with a PPI [28]. Although a PPI was not routinely used in addition to the NSAID (loxoprofen sodium) in this study, no serious GI events were noted.

Since chronic kidney disease (CKD), which is similar to knee OA, is also a prevalent disease especially in older populations, knee OA patients with CKD may have a different risk profile and treatment response than knee OA patients without CKD. However, as patients with renal disorders were excluded in the present study, as described in the Methods section, whether the presence of CKD has any effect on the efficacy and safety of either the IA-HA or NASIDs remains unclear.

The efficacy of IA-HA for knee OA has been debated for over a decade. Although it has been systemically evaluated in meta-analyses, most previous studies have focused on comparing the findings with either placebo or intra-articular corticosteroids [9,10,29]. No previous studies have undertaken a meta-analysis with NSAIDs, which is one of the most efficacious and widely used treatments for knee OA [5]. The present study clearly shows that IA-HA is as effective as continuous NSAID use at five weeks of treatment, and, in addition, it showed a more favorable safety profile of IA-HA over NSAIDs for knee OA. The present study suggests that future randomized trials should thus be carried out with a longer duration of follow-up and larger samples, in order to identify optimal knee OA treatment alternatives. Furthermore, it would also be interesting to evaluate whether any synergistic effect of these two combined treatments exists when they are combined.

The current study does have some limitations. First, this investigation was an open-label randomized trial and not a double-blind controlled trial. Therefore, the design may have introduced certain bias into the results. Second, the trial's size was calculated to have sufficient power to exclude a 10% between-group percentage change of JKOM score, which can be debated. This margin was supported by our pilot study, as described previously. Third, in subgroup analysis for the patients with a K/L grade of 1, IA-HA treatment reduced the JKOM score. However, this reduction was not statistically significant ($P = 0.058$). Although the reason for this is unclear, the interpretation of the result was limited by the small number of patients (n = 15) and, therefore, it may be one of the limitations. Even though some subjects had a K/L grade of 1, some have an increased risk for rapid progression of the disease [30]. Unfortunately, we cannot predict radiographically who is at risk for progression [4].

Conclusions

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

Abbreviations

ACR: American College of Rheumatology; BMI: body mass index; CKD: chronic kidney disease; FAS: full analysis set; GI: gastrointestinal; HA: hyaluronic acid; IA-HA: intra-articular injections of HA; JKOM: Japanese Knee Osteoarthritis Measure; K/L: Kellgren-Lawrence; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology Clinical Trials; PPI: proton pump inhibitor; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

As principal investigators of this study, all authors of this study had full access to all data, and take responsibility for their integrity and the accuracy of their analysis. TN, KS, KH, HKu and KK participated in the study design. HKu and KK supervised the study. MI, TN, KS, HKi, SS, GO, TY, YU, JC, MK and HKu collected the data. MI, YI and KH analyzed the data. YI and KH provided statistical expertise. MI and KH drafted the manuscript, and the manuscript was revised for content by MI, TN, KS, KH, HKi, SS, GO, TY, YU, JC, YI, MK, HKu and KK. All authors read and approved the final manuscript.

Acknowledgements

The authors thank all investigators involved in this study at the following medical facilities listed in alphabetical order: Gifu University Hospital (Gifu, Japan), Heisei Memorial Hospital (Shimane, Japan), Izumo Citizens Hospital (Shimane, Japan), Izumo General Medical Center (Shimane, Japan), Juntendo University Medical Center (Tokyo, Japan), Juntendo University Nerima Hospital (Tokyo, Japan), Ken-ai Memorial Hospital (Fukuoka, Japan), Kinki University Sakai Hospital (Osaka, Japan), Kitanarashino Hanawa Hospital (Chiba, Japan), Nara Hospital Kinki University Faculty of Medicine (Ikoma, Japan), Niigata University Hospital (Niigata, Japan), Niigata Rehabilitation Hospital (Niigata, Japan), Nishimino-Kosei Hospital (Gifu, Japan), Nishi-Niigata Chuo National Hospital (Niigata, Japan), Occupational and Environmental Health University Hospital (Kitakyusyu, Japan), Shimane University Hospital (Shimane, Japan), Sapporo Daiichi Hospital (Hokkaido, Japan), Sapporo Medical University Hospital (Hokkaido, Japan), Tokyo Women's Medical University Medical Center East (Tokyo, Japan), and Tama Nannbu Chiiki Hospital (Tokyo, Japan).

The authors also express sincere thanks to Dr. Fumie Tokuda and Dr. Chizuko Wakabayashi at the coordinating data center (Gunma University, Gunma, Japan) for their help with data management and data analysis. We also express our appreciation to Dr. Yoshihiko Yamada, Dr. A. Robin Poole and Dr. Joe Matsuoka for their helpful comments and suggestions.

Author details
[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. [2]Department of Orthopaedic Surgery, University of Occupational and Environmental Health, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. [3]Department of Orthopaedic Surgery, Gifu University, School of Medicine, 1-1, Yanagido, Gifu City 501-1193, Japan. [4]Department of Basic Medical Sciences, School of Health Sciences, Faculty of Medicine, Gunma University, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan. [5]Department of Orthopaedic Surgery, Sakai Hospital Kinki University Faculty of Medicine, 2-7-1, Harayamadai, Minami-ku, Sakai-city 590-0132, Osaka, Japan. [6]Department of Orthopaedic Surgery and Rheumatology, Nara Hospital Kinki University Faculty of Medicine, 1481-1, Otodacho, Ikoma, Nara 630-0293, Japan. [7]Department of Health and Sports, Niigata University of Health and Welfare, 1398, Shimamicho, Niigata Kita-ku, Niigata 950-3198, Japan. [8]Department of Orthopaedic Surgery, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-8543, Japan. [9]Department of Orthopaedics, Shimane University, School of Medicine, 89-1, Enya-cho, Izumo-shi, Shimane 693-8501, Japan. [10]Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East, 2-1-10, Nishiogu, Arakawa, Tokyo 116-8567, Japan.

Received: 2 June 2013 Accepted: 8 January 2014
Published: 21 January 2014

References

1. Dieppe PA, Lohmander LS: **Pathogenesis and management of pain in osteoarthritis.** *Lancet* 2005, **365**:965–973.
2. Felson DT: **Clinical practice, Osteoarthritis of the knee.** *N Engl J Med* 2006, **354**:841–848.
3. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ: **Knee replacement.** *Lancet* 2012, **379**:1331–1340.
4. Ishijima M, Watari T, Naito K, Kaneko H, Futami I, Yoshimura-Ishida K, Tomonaga A, Yamaguchi H, Yamamoto T, Nagaoka I, Kurosawa H, Poole RA, Kaneko K: **Relationships between biomarkers of cartilage, bone, synovial metabolism and knee pain provide insights into the origins of pain in early knee osteoarthritis.** *Arthritis Res Ther* 2011, **13**:R22.
5. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P: **OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009.** *Osteoarthritis Cartilage* 2010, **18**:476–499.
6. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P: **OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence.** *Osteoarthritis Cartilage* 2007, **15**:981–1000.
7. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P: **OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines.** *Osteoarthritis Cartilage* 2008, **16**:137–162.
8. Lo GH, LaValley M, McAlindon T, Felson DT: **Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis.** *JAMA* 2003, **290**:3115–3121.
9. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE: **Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis.** *Arthritis Rheum* 2009, **61**:1704–1711.
10. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE: **Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis.** *Osteoarthritis Cartilage* 2011, **19**:611–619.
11. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S: **Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis.** *Ann Intern Med* 2012, **157**:180–191.
12. **UMIN Clinical Trials Registry.** [http://www.umin.ac.jp/ctr/index.htm]
13. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M, Howell D, Kaplan D, Koopman W, Longley S III, Mankin H, McShane DJ, Medsger T Jr, Meenan R, Mikkleson W, Moskowitz R, Murphy W, Rothschild B, Segal M, Sokoloff L, Wolfe F: **Development of criteria for the classification and reporting of osteoarthritis, Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.** *Arthritis Rheum* 1986, **29**:1039–1049.
14. Kellgren JH, Lawrence JS: **Radiological assessment of osteo-arthrosis.** *Ann Rheum Dis* 1957, **16**:494–502.
15. Akai M, Doi T, Fujino K, Iwaya T, Kurosawa H, Nasu T: **An outcome measure for Japanese people with knee osteoarthritis.** *J Rheumatol* 2005, **32**:1524–1532.
16. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M: **OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited.** *Osteoarthritis Cartilage* 2004, **12**:389–399.
17. Kawasaki T, Kurosawa H, Ikeda H, Takazawa Y, Ishijima M, Kubota M, Kajihara H, Maruyama Y, Kim SG, Kanazawa H, Doi T: **Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial.** *J Orthop Sci* 2009, **14**:182–191.
18. Kubota M, Ishijima M, Kurosawa H, Liu L, Ikeda H, Osawa A, Takazawa Y, Kawasaki T, Saita Y, Kimura Y, Kaneko K: **A longitudinal study of the relationship between the status of bone marrow abnormalities and progression of knee osteoarthritis.** *J Orthop Sci* 2010, **15**:641–646.
19. Julovi SM, Ito H, Nishitani K, Jackson CJ, Nakamura T: **Hyaluronan inhibits matrix metalloproteinase-13 in human arthritic chondrocytes via CD44 and P38.** *J Orthop Res* 2011, **29**:258–264.
20. Conrozier T, Balblanc JC, Richette P, Mulleman D, Maillet B, Henrotin Y, Rannou F, Piroth C, Hilliquin P, Mathieu P, Walliser-Lohse A, Rousselot I, Plattner V, Maillefert JF, Vignon E, Chevalier X: **Early effect of hyaluronic acid intra-articular injections on serum and urine biomarkers in patients with knee osteoarthritis: an open-label observational prospective study.** *J Orthop Res* 2012, **30**:679–685.
21. Reichenbach S, Blank S, Rutjes AW, Shang A, King EA, Dieppe PA, Juni P, Trelle S: **Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis.** *Arthritis Rheum* 2007, **57**:1410–1418.
22. Goldring MB, Goldring SR: **Osteoarthritis.** *J Cell Physiol* 2007, **213**:626–634.
23. Liu L, Ishijima M, Futami I, Kaneko H, Kubota M, Kawasaki T, Matsumoto T, Kurihara H, Ning L, Xu Z, Ikeda H, Takazawa Y, Saita Y, Kimura Y, Xu S, Kaneko K, Kurosawa H: **Correlation between synovitis detected on enhanced-magnetic resonance imaging and a histological analysis with a patient-oriented outcome measure for Japanese patients with end-stage knee osteoarthritis receiving joint replacement surgery.** *Clin Rheumatol* 2010, **29**:1185–1190.
24. Yatabe T, Mochizuki S, Takizawa M, Chijiiwa M, Okada A, Kimura T, Fujita Y, Matsumoto H, Toyama Y, Okada Y: **Hyaluronan inhibits expression of ADAMTS4 (aggrecanase-1) in human osteoarthritic chondrocytes.** *Ann Rheum Dis* 2009, **68**:1051–1058.
25. Plaas A, Li J, Riesco J, Das R, Sandy JD, Harrison A: **Intraarticular injection of hyaluronan prevents cartilage erosion, periarticular fibrosis and mechanical allodynia and normalizes stance time in murine knee osteoarthritis.** *Arthritis Res Ther* 2011, **13**:R46.
26. Ning L, Ishijima M, Kaneko H, Kurihara H, Arikawa-Hirasawa E, Kubota M, Liu L, Xu Z, Futami I, Yusup A, Miyahara K, Xu S, Kaneko K, Kurosawa H: **Correlations between both the expression levels of inflammatory mediators and growth factor in medial perimeniscal synovial tissue and the severity of medial knee osteoarthritis.** *Int Orthop* 2011, **35**:831–838.
27. Goldberg VM, Buckwalter JA: **Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity.** *Osteoarthritis Cartilage* 2005, **13**:216–224.
28. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D: **Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada.** *Am J Gastroenterol* 2008, **103**:872–882.
29. McAlindon TE, Bannuru RR: **Osteoarthritis: Is viscosupplementation really so unsafe for knee OA?** *Nat Rev Rheumatol* 2012, **8**:635–636.
30. Hart DJ, Spector TD: **Kellgren & Lawrence grade 1 osteophytes in the knee–doubtful or definite?** *Osteoarthritis Cartilage* 2003, **11**:149–150.

doi:10.1186/ar4446
Cite this article as: Ishijima *et al.*: 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. *Arthritis Research & Therapy* 2014 **16**:R18.

Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-013-2767-6

KNEE

Kinematics of the knee after unicompartmental arthroplasty is not the same as normal and is similar to the kinematics of the knee with osteoarthritis

Tomoharu Mochizuki · Takashi Sato · John David Blaha · Osamu Tanifuji · Koichi Kobayashi · Hiroshi Yamagiwa · Satoshi Watanabe · Munenori Matsueda · Yoshio Koga · Go Omori · Naoto Endo

Received: 4 December 2012 / Accepted: 30 October 2013

Abstract
Purpose It is common to assert that restoration of normal knee kinematics is essential for the best functional result after knee arthroplasty. Previous studies using the progression of the geometric centre axis have suggested that kinematics after unicompartmental arthroplasty is markedly different from the normal. For this study, the transepicondylar axis was used because this axis is closer to the flexion axis and should be a better reference for motion. The following hypothesis was tested: the transepicondylar axis would again show that the postoperative kinematics does not restore normal motion and is closer to that before replacement.
Methods Seventeen osteoarthritic knees were tested before and after unicompartmental arthroplasty using a three-dimensional to two-dimensional registration technique tracking the transepicondylar axis to calculate translation and rotation of this axis. Results were compared for the seventeen knees before and after arthroplasty and were compared to the normal knee as measured in our previous study.
Results Similar motion patterns in the pre- and postoperative knees were shown but both the pre- and postoperative motion were markedly different from the normal knee.
Conclusions This result supported our hypothesis. The clinical relevance is that medial unicompartmental arthroplasty cannot restore the motion of the knee to normal in the living knee. Therefore, it would be expected that the patient for unicompartmental knee might not feel normal. It may not be possible depending on ligaments alone to restore the knee to normal, and the changes in the articular shapes and the surgical procedure may also be necessary.
Level of evidence IV.

Keywords Knee kinematics · Transepicondylar axis · 3D to 2D registration · Squatting · Unicompartmental knee arthroplasty

T. Mochizuki (✉) · O. Tanifuji · H. Yamagiwa · N. Endo
Department of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Science, 1-757 Asahimachi-dori Chuo-ku, Niigata City, Niigata 951-8510, Japan
e-mail: tomo07301977@yahoo.co.jp

T. Mochizuki · J. D. Blaha
Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA

T. Mochizuki · T. Sato · S. Watanabe · Y. Koga
Department of Orthopaedic Surgery, Niigata Medical Center, Niigata, Japan

K. Kobayashi
Department of Health Sciences, Niigata University School of Medicine, Niigata, Japan

M. Matsueda
Department of Orthopaedic Surgery, Niigata Central Hospital, Niigata, Japan

G. Omori
Center for Transdisciplinary Research, Institute for Research Promotion, Niigata University, Niigata, Japan

Introduction

It has been asserted that the kinematics of the knee after unicompartmental arthroplasty (UKA) is close to that of a normal knee because the anterior (ACL) and posterior cruciate ligaments (PCL) are preserved [16]. This is

Published online: 12 November 2013

presented as one of the key advantages of UKA over tricompartmental arthroplasty (TKA) based on the argument that the proprioception, satisfaction and function of the knee would be better because of the near normal kinematics [2, 7, 17].

In cadaver studies, the motion of the knee following UKA has been reported to be close to normal [16]. Our previous in vivo study in which we tracked the geometric centre axis (GCA—a line between the centres of the best-fit spheres of the medial and lateral posterior condyles [13, 19]) showed that the kinematics after medial UKA was different from the normal knee and closer to the same knee before the arthroplasty (i.e., the same knee with medial OA) than to the normal knee [14, 19]. However, use of the GCA might give a false measurement of kinematics because this axis is not the flexion axis and thus will translate relative to the flexion axis as the knee moves. Since the transepicondylar axis (TEA) is generally thought to be closer to the flexion axis than the GCA (Fig. 1) [1, 5, 9], with this experiment it was sought to determine the kinematics of the knee using the TEA, with the hypothesis that the kinematics measured by using the TEA would again show that UKA does not restore normal motion and that the kinematics after UKA is closer to that before replacement [14]. If this hypothesis is correct, the clinical relevance is that medial UKA cannot restore the motion of the knee to normal in the living knee. Therefore, it would be expected that the patient for UKA might not feel normal. It may not be possible depending on ligaments alone to restore the knee to normal, and the changes in the articular shapes and the surgical procedure may also be necessary.

Materials and methods

The kinematics of 17 knees (14 patients), which had been treated with a medial UKA (Zimmer Unicompartmental High-Flex Knee System (ZUK), Zimmer Inc., Warsaw, IN, USA), were examined. These knees and patients are the same group that formed the basis for our previous report [14]. The patient demographic data are shown in Table 1.

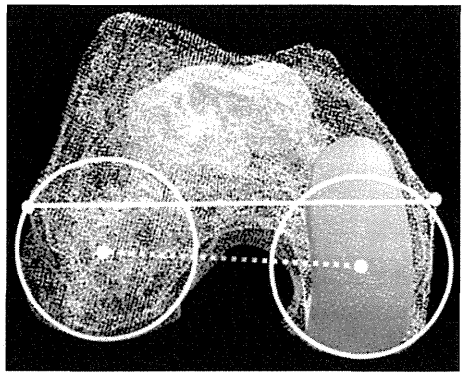

Fig. 1 Transepicondylar axis (TEA) and the geometric centre axis (GCA)

In all knees, the presence of a normal-appearing ACL was confirmed at the time of the surgery. The proximal tibia was resected so that the cut surface was perpendicular to the tibial shaft in the coronal plane, with a 7° posterior inclination in the sagittal plane. The distal femur was cut using an intramedullary alignment rod, and the posterior femur was cut according to the implant thickness. The polyethylene insert thickness was selected so that the mechanical axis would be slightly medial to the knee centre (i.e., slight varus alignment). To assure proper alignment for each case, the postoperative femorotibial angle (FTA) was measured from the three-dimensional (3D) model (described below) under a weight-bearing condition [12, 18]. Five degrees or less of varus alignment (185°) and no severe valgus alignment (<170°) were considered satisfactory for inclusion in the analysis.

Computed tomography (CT) (SOMATOM Sensation 16; Siemens Inc., Munich, Germany) scans were obtained with a 1-mm interval. A 3D digital model of the femur and tibia was reconstructed using a 3D visualization and modelling software program (ZedView; LEXI Inc., Tokyo, Japan).

A squatting motion from standing to maximum flexion was recorded using a flat panel detector (AXIOM Artis® dTA; Siemens, Inc.) or a single-plane fluoroscopic system (ADVANTX UN, GE Yokogawa Medical System, Tokyo, Japan). The sampling frequency, image area and image resolution were based on our previous study [11, 14, 19, 20]. Using the grid pattern, the distortion of the fluoroscopic image was corrected employing a cubic polynomial equation [8, 11]. The knee motions were recorded before and at least 6 months after UKA.

The kinematics for the preoperative knees was analysed using the 3D-to-2D image registration technique via an automated shape-matching algorithm that used single-plane fluoroscopic images as reported by Kobayashi et al. [11]. This is the method to estimate the 3D posture (6 degree-of-freedom (DOF) parameters) by matching the

Table 1 Patient demographics

	Medians (range)
Age (years)	77 (62–82)
Follow-up term (months)	24 (7–39)
Body mass index (BMI)	25.6 (18.7–28.9)
Radiographic level of OA [10]	4 (3–4)

Radiographic level of osteoarthritis (OA) was determined based on Kellgren–Lawrence system [10]

calculated projection of the bone 3D model with the silhouette of the bone observed in 2D fluoroscopic images. The accuracy was confirmed by comparing the estimated value from this method with the true values measured by using a 3D coordinated measuring machine. The accuracy was calculated by the root mean square error (RMSE), which was 0.3–0.8 mm for in-plane translation, 2.2 mm for out-of-plane translation and 0.2°–0.6° for rotation [11].

The anatomical coordinate system was automatically established according to the definitions reported by Sato et al. [18] as follows: the tibial Z-axis (positive superiorly) was defined by a line connecting the midpoint of the tibial eminences and the midpoint of the medial and lateral top of the talar dome. The tibial Y-axis (positive anteriorly) was defined as the line drawn from the mediolateral centre of the tibial insertion of the posterior cruciate ligament that is perpendicular to the Z-axis. The tibial X-axis (positive right) was defined as the cross product of the *Z*-axis and *Y*-axis. The *XY* plane in this coordinate system was defined as the tibial axial plane.

Postoperative relative motion between femur and tibia was automatically obtained by combining the 3D component alignment data, using a 3D-to-2D image registration technique via calibrated biplanar static radiography (Fig. 2) [12, 14, 18], with the relative motion between both components, using a 3D-to-2D image registration technique via the single-plane fluoroscopic images (Fig. 2). Kobayashi et al. [12] calculated the accuracy by RMSE, which was 0.3–0.6 mm for in-plane translation, 0.1–0.7 mm for out-of-plane translation and 0.1°–0.7° for rotation in biplanar 3D-to-2D image registration and was 0.3–0.7 mm for in-plane translation, 0.2–0.7 mm for out-of-plane translation and 0.2°–0.8° for rotation in combining biplanar with single-planar 3D-to-2D image registration [14].

The TEA was defined as a line connecting the two peak points of both femoral condyles (clinical epicondylar axis, CEA) based on the method described by Most et al. [15] (Fig. 1). The TEA projection onto the tibial surface was then evaluated as (1) the rotation angle relative to the tibia and (2) the anteroposterior (AP) location and translation of the medial and lateral ends of the TEA relative to the tibia in the range 10–100° of knee flexion.

The reproducibility of this measurement was previously reported by Tanifuji et al. [20]. The intra-class correlation coefficient (ICC) of the rotation angle, the AP location of the medial end and that of the lateral end were 0.98, 0.91 and 0.85, respectively. The inter-class correlation coefficient (ICC) of the rotation angle, the AP location of the medial end and that of the lateral end were 0.92, 0.86 and 0.99, respectively.

This study was performed according to the protocol approved by the Institutional Review Board (IRB) of

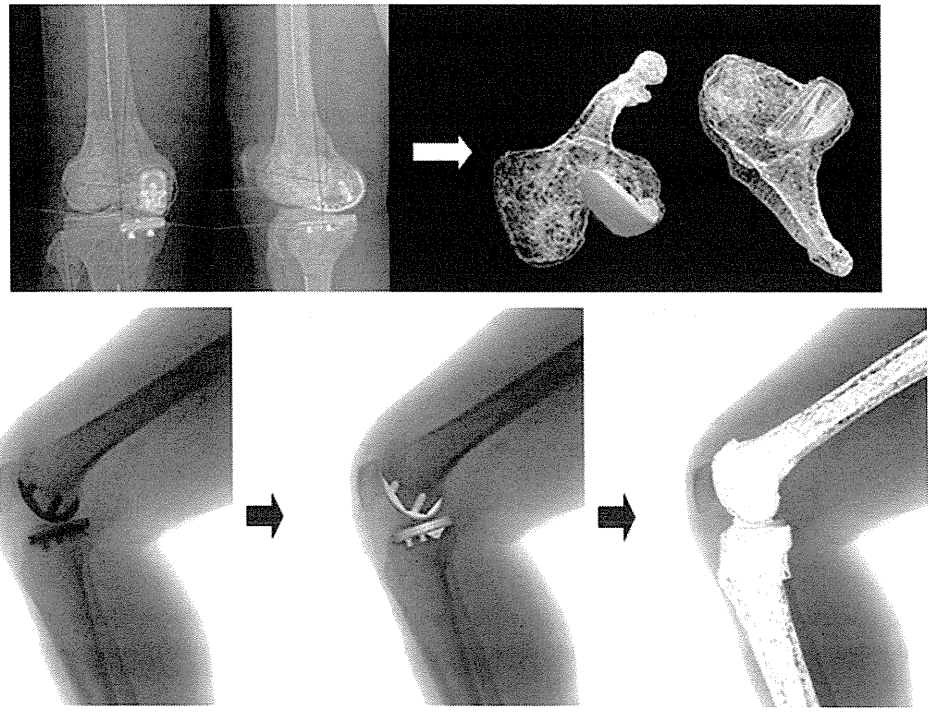

Fig. 2 Three-dimensional component alignment to the bone was first obtained using calibrated biplanar static radiography. The relative motion between the two components was subsequently evaluated via the 3D-to-2D image registration technique. Then, by combining the 3D component alignment data with the relative motion between the two components, the postoperative relative motion between the bones could be automatically obtained

Table 2 Comparison among three groups for 10°–100° of knee flexion

Parameter	FER (degrees) Medians (range)	AP location (mm) Medians (range)		AP translation (mm) Medians (range)	
		Medial	Lateral	Medial	Lateral
Pre-UKA	5.7 (−9.6 to 20.3)	−9.5 (−23.6 to 0.9)	−13.6 (−24.6 to −1.9)	−10.8 (−19.8 to 1.1)	−18.4 (−29.0 to −2.3)
Post-UKA	3.4 (−7.7 to 13.7)	−9.9 (−17.3 to −2.8)	−14.0 (−21.0 to −0.2)	−11.2 (−14.3 to −6.6)	−13.2 (−21.3 to −3.5)
Normal [20]	8.0 (−3.4 to 19.0)	−5.7 (−12.7 to 5.3)	−18.5 (−24.9 to −6.0)	−6.3 (−15.5 to 1.8)	−17.9 (−29.6 to −5.8)

The AP location is described by the medians of the coordinate value in 100° of knee flexion; the AP translation shows that minus (−) means posterior translation

FER femoral external rotation angles, *AP location* anteroposterior location, *AP translation* anteroposterior translation

Table 3 Statistical analysis

Parameter	FER	AP location		AP translation	
		Medial	Lateral	Medial	Lateral
Pre versus post					
p value	n.s.	n.s.	n.s.	n.s.	0.019
Power	0.381	0.074	0.069	0.238	0.692
Normal [20] versus pre					
p value	0.041	0.031	0.026	n.s.	0.026
Power	0.540	0.592	0.621	0.320	0.618
Normal [20] versus post					
p value	<0.001	0.004	0.030	<0.001	<0.001
Power	0.992	0.858	0.593	0.979	0.999

n.s. = $p > 0.05$; *FER* femoral external rotation angles, *AP location* anteroposterior location, *AP translation* anteroposterior translation

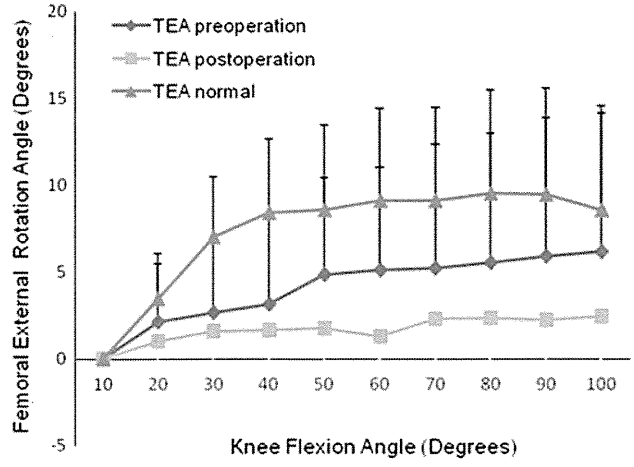

Fig. 3 Normal, pre- and postoperative femoral external rotation angles relative to the tibia as determined via the TEA for 10–100° of knee flexion

Niigata University, and the ID number of the approval was 977.

Statistical analysis

Data were analysed by comparing the motion of each of these subjects' knees before and after implantation of the UKA and in aggregate to the normal knee data found by Tanifuji et al. [20].

Two-way repeated-measures ANOVA and a post hoc power analysis were employed to analyse the differences in parameters among each group (SPSS version 20). Statistical significance was defined as $P < 0.05$.

Results

The femorotibial angle (FTA) in a standing position changed from varus alignment, as expected for medial compartment OA, to satisfactory alignment in all cases, and all were included in the analysis (pre: median 184.2°, range 178.7°–192.8°; post: median 180.6°, range 172.5°–184.6°).

The pre- and postoperative total external rotation angles of the TEA relative to the tibia for 10°–100° of knee flexion are shown in Tables 2, 3 and Fig. 3. The TEA showed consistent external rotation before and after UKA. The postoperative total external rotation angles over the entire flexion tended to decrease compared to the preoperative angles, but with no statistically significant difference.

The AP locations and translations of the medial and lateral ends of the TEA relative to the tibia for 10–100° of knee flexion are shown in Tables 2, 3 and Figs. 4, 5, 6, 7. The pre- and postoperative locations and translation of the medial end of the TEA were similar and not significantly different (Table 2, 3; Figs. 4, 5). The lateral end of the TEA demonstrated consistently posterior translation throughout knee flexion before and after UKA. The postoperative posterior translation of the lateral end of the TEA was significantly lower than the preoperative value (Tables 2, 3; Fig. 7).

Compared to the normal data of our previous study (Tables 2, 3; Figs. 3, 4, 5, 6, 7) [20], the preoperative evaluation parameters except for the medial translation

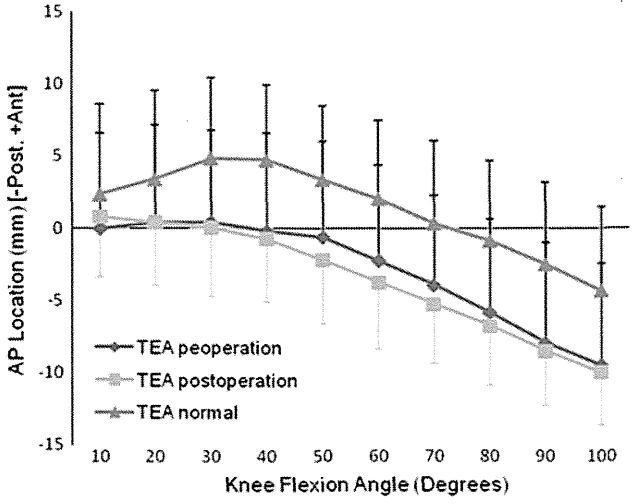

Fig. 4 Normal, pre- and postoperative AP locations of the medial femoral ends of the TEA relative to the tibia for 10–100° knee of flexion

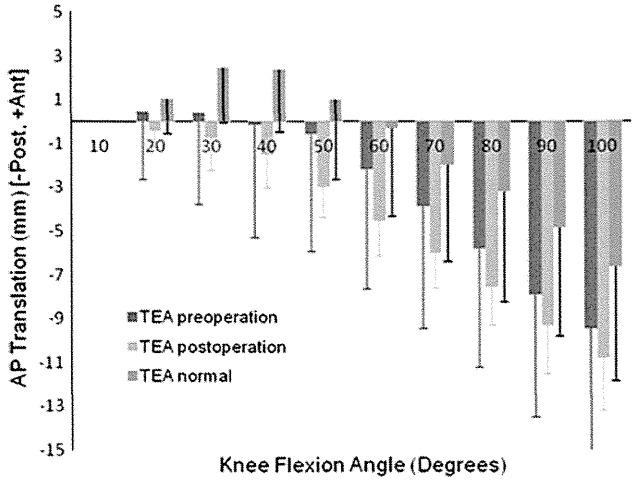

Fig. 5 Normal, pre- and postoperative AP translations of the medial femoral ends of the TEA relative to the tibia for 10–100° knee flexion

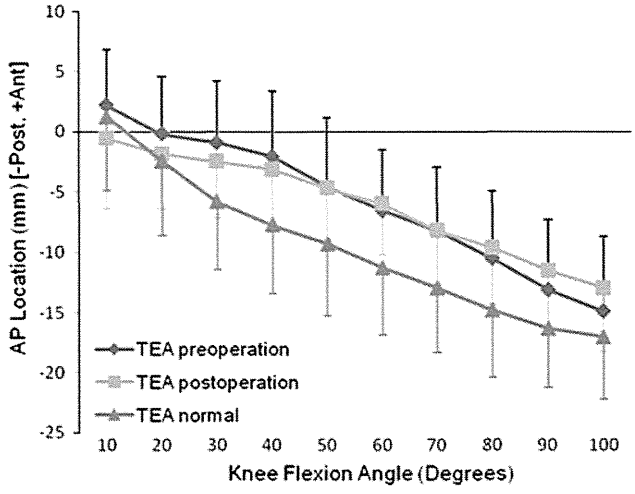

Fig. 6 Normal, pre- and postoperative AP locations of the lateral femoral ends of the TEA relative to the tibia for 10–100° knee flexion

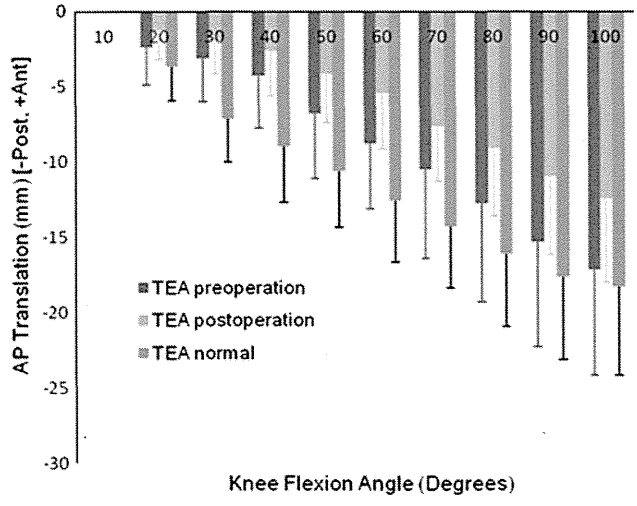

Fig. 7 Normal, pre- and postoperative AP translations of the lateral femoral ends of the TEA relative to the tibia for 10–100° knee flexion

were significantly different. All of the postoperative evaluation parameters were significantly different from those of the normal.

Discussion

The most important finding of the present study was that the kinematics measured by using the TEA projected onto the tibia showed that the UKA did not restore the motion of the knee to normal and was closer to that before replacement than to normal, and our hypothesis was supported.

While the motion pattern of the TEA for the OA knees was similar to that for the normal knees [20], the magnitude of each kinematic parameter for the OA knees decreased compared with that for the normal knees (Tables 2, 3). These differences might be caused by the geometric changes to the arthritic surfaces and inadequate function of the ACL, which in this study was confirmed visually at the time of surgery [14]. However, it is also possible that the kinematics of a knee is part of the pathology of OA and that OA knees never exhibited "normal" kinematics but were always "abnormal" and that abnormal motion caused the OA.

Patil et al. [16] reported that UKA preserved normal knee kinematics in the cadaver study implying that the cruciate ligaments, left in place with UKA, would direct this motion. However, in our study using the projection of the TEA onto the tibia, in vivo knee motion after UKA

showed significant differences in all the evaluation parameters compared to the normal knee. This result indicates that medial UKA does not restore the motion of the knee to normal in the living knee. Furthermore, our data showed that the postoperative kinematics was more similar to that for the osteoarthritic knee for which UKA was performed. This fact implies that the postoperative motion is affected by the preoperative condition depending on patient selection criteria for UKA, and thus, patient selection criteria for UKA are one of the important factors to reproduce normal knee kinematics.

Blaha et al. [3, 4] have suggested that anteroposterior (AP) stability of the medial side for TKA is a key factor in replicating medial stability and medial pivot motion similar to the normal. To accomplish this, they suggest a TKA designed with a high-conformity ball-in-socket geometry on the medial side. The design of the fixed medial UKA used in this study has low conformity to theoretically decrease constraint and minimize wear. This lack of conformity decreases the AP stability, thus eliminating the rotatory fulcrum on the medial side, and suggests an explanation for the motion of the medial side of the TEA in this study. Our data suggest that, with an unconstrained medial side, the ACL in these UKA knees is inadequate to control AP motion and to induce femoral external rotation in response to the environment of the UKA knee (i.e. the alignment, soft tissue tension, stabilizing and/or accelerating muscular function and residual pain).

This study had several limitations that should be kept in mind when interpreting the results. First, since the mean follow-up term was relatively short, the relationships between the pre- and postoperative knee kinematics and long-term clinical outcomes are unknown. Second, the number of patients of this study was too small to even begin to characterize what patient or surgical factors might contribute to altered kinematics. For example, in this study the tibial cut surface was perpendicular to the tibial shaft in the coronal plane (as is suggested in the surgical technique), but it has been recently reported that the tibial cut surface should be cut differently, "parallel to the joint line" because UKA should correct only the intra-articular deformity [6].

The clinical relevance of this work is that medial UKA cannot restore the motion of the knee to normal in the living knee, and therefore, clinical results could be improved by changes in design, technique, or both, and patient selection criteria to achieve more normal kinematics.

Conclusions

The result of this study indicates that the kinematics for medial UKA does not restore normal kinematics but rather establishes motion closer to that of OA knees.

Acknowledgments This study would have been impossible without the cooperation of the Department of Radiology, Niigata Medical Center and Niigata University Hospital. The authors would like to thank all staff members of the department. The authors would also like to thank all staff members of LEXI Corporation, Tokyo, Japan, for their technical support.

Conflict of interest The authors did not receive and will not receive any benefits or funding from any commercial party related directly or indirectly to the subject of this article.

References

1. Asano T, Akagi M, Nakamura T (2005) The functional flexion-extension axis of the knee corresponds to the surgical epicondylar axis: in vivo analysis using a biplanar image matching technique. J Arthroplasty 20:1060–1067
2. Bae DK, Song SJ, Cho SD (2011) Clinical outcome of total knee arthroplasty with medial pivot prosthesis a comparative study between the cruciate retaining and sacrificing. J Arthroplasty 26:693–698
3. Blaha JD (2002) A medial pivot geometry. Orthopedics 25: 963–964
4. Blaha JD (2004) The rationale for a total knee implant that confers anteroposterior stability throughout range of motion. J Arthroplasty 19:22–26
5. Churchill DL, Incavo SJ, Johnson CC, Beynnon BD (1998) The transepicondylar axis approximates the optimal flexion axis of the knee. Clin Orthop Relat Res 356:111–118
6. Deschamps G, Chol C (2011) Fixed-bearing unicompartmental knee arthroplasty. Patients' selection and operative technique. Orthop Traumatol Surg Res 97:648–661
7. Fan CY, Hsieh JT, Hsieh MS, Shih YC, Lee CH (2010) Primitive results after medial-pivot knee arthroplasties: a minimum 5-year follow-up study. J Arthroplasty 25:492–496
8. Haaker P, Klotz E, Koppe R, Linde R (1990/1991) Real-time distortion correction of digital X-ray 2/TV-systems an application example for digital flashing tomosynthesis (DFTS). Int J Cardiac Imaging 6:36–45
9. Hollister AM, Jatana A, Singh AK, Sullivan WW, Lupichuk AG (1993) The axes of rotation of the knee. Clin Orthop Relat Res 290:259–268
10. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteoarthritis. Ann Rheum Dis 16:494–502
11. Kobayashi K, Tanaka N, Odagawa K, Sakamoto M, Tanabe Y (2009) Image-based matching for natural knee kinematics measurement using single-plane fluoroscopy. J Jpn Soc Exp Mech 9: 162–166
12. Kobayashi K, Sakamoto K, Tanabe Y, Ariumi A, Sato T, Omori G, Koga Y (2009) Automated image registration for three-dimensional alig nment of entire lower extremity and implant position using bi-plane radiography. J Biomech 42:2818–2822
13. Kurosawa H, Walker PS, Abe S, Garg A, Hunter T (1985) Geometry and motion of the knee for implant and orthotic design. J Biomech 18:487–499
14. Mochizuki T, Sato T, Tanifuji O, Kobayashi K, Koga Y, Yamagiwa H, Omori G, Endo N (2012) In vivo pre- and postoperative three-dimensional knee kinematics in unicompartmental knee arthroplasty. J Orthop Sci. doi:10.1007/s0077601203229
15. Most E, Axe J, Rubash H, Li G (2004) Sensitivity of the knee joint kinematics calculation to selection of flexion axes. J Biomech 37:1743–1748
16. Patil S, Colwell CW Jr, Ezzet KA, D'Lima DD (2005) Can normal knee kinematics be restored with unicompartmental knee replacement? J Bone Joint Surg Am 87:332–338

17. Pritchett JW (2011) Patients prefer a bicruciate-retaining or the medial pivot total knee prosthesis. J Arthroplasty 26:224–228
18. Sato T, Koga Y, Omori G (2004) Three-dimensional lower extremity alignment assessment system. J Arthroplasty 19:620–628
19. Tanifuji O, Sato T, Kobayashi K, Mochizuki T, Koga Y, Yamagiwa H, Omori G, Endo N (2011) Three-dimensional in vivo motion analysis of normal knees using single-plane fluoroscopy. J Orthop Sci 16:710–718
20. Tanifuji O, Sato T, Kobayashi K, Mochizuki T, Koga Y, Yamagiwa H, Omori G, Endo N (2012) Three-dimensional in vivo motion analysis of normal knees employing transepicondylar axis as an evaluation parameter. Knee Surg Sports Traumatol Arthrosc. doi:10.1007/s001670122010x

J Orthop Sci
DOI 10.1007/s00776-014-0535-1

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

Received: 22 March 2013 / Accepted: 15 January 2014

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

Published online: 07 February 2014

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

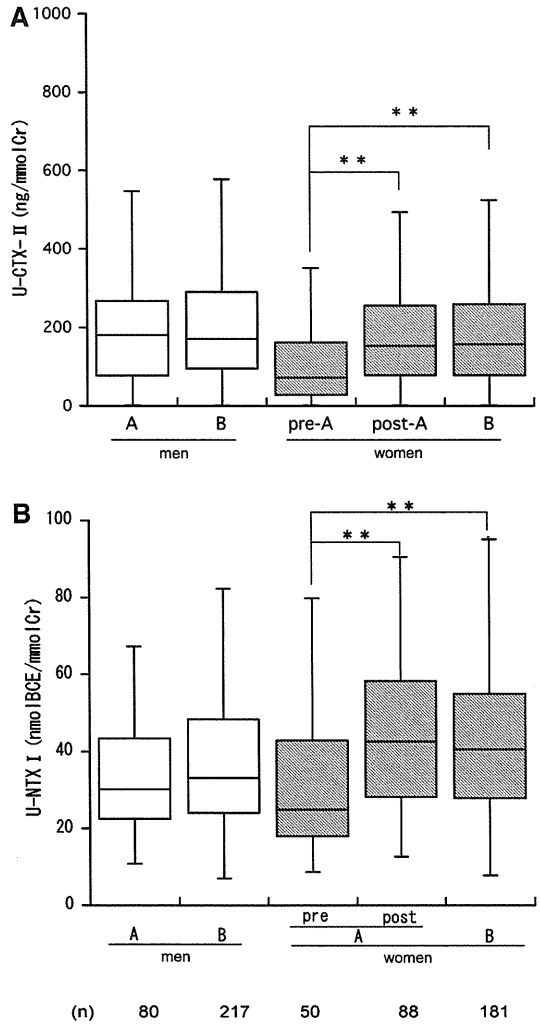

Fig. 1 The relationship between the age and uCTX-II level in the non-OA group (knee X-ray OA grade 0 and 1) subjects. **a** Subjects aged 40–59 years, **b** 60–79 years. *pre* pre-menopausal, *post* post-menopausal. The numbers of subjects are shown at the *bottom* **b**. Each *box* represents the 25th/50th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

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).

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

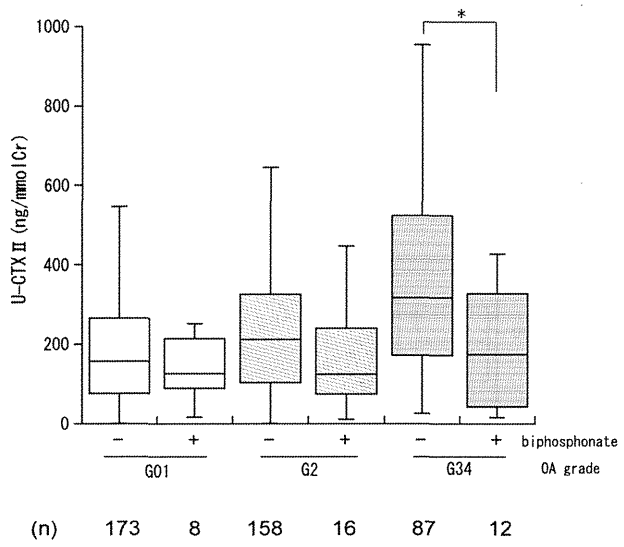

Fig. 2 The influence of oral bisphosphonate use on the uCTX-II levels in the different OA grade groups of 60-year-old to 79-year-old female subjects. The numbers of subjects in each group are shown at the *bottom* of the figure. $*p < 0.05$

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.

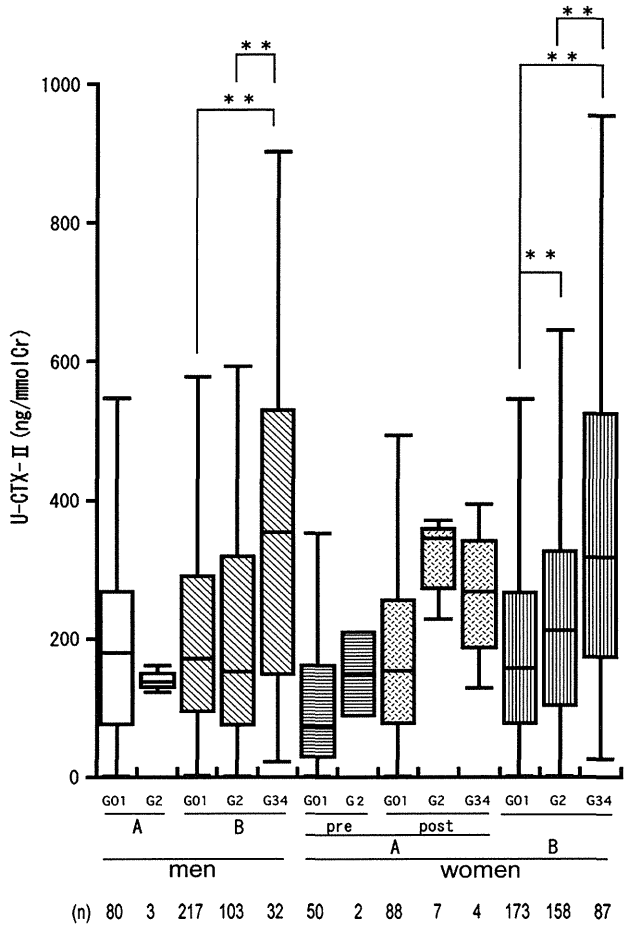

Fig. 3 The relationship between the knee X-ray OA grade and uCTX- II level. **a** Subjects aged 40–59 years, **b** 60–79 years. *pre* pre-menopausal, *post* post-menopausal. The numbers of subjects are shown at the *bottom* of the *panels*. A statistical analysis was performed to examine the differences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

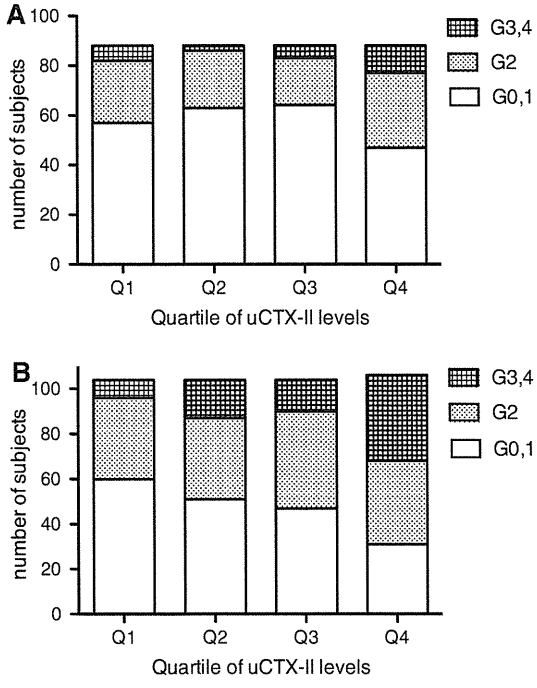

Fig. 4 There was an increased uCTX-II level and distribution of OA grades in 60–79 year-old **a** male ($n = 352$) and **b** female ($n = 418$) subjects. The mean values of uCTX-II (ng/mmol Cr) for each quartile from Q1–4 were 42.6, 130.3, 237.7, and 548.8 in males, and 49.4, 151.8, 262.6, and 532.3 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

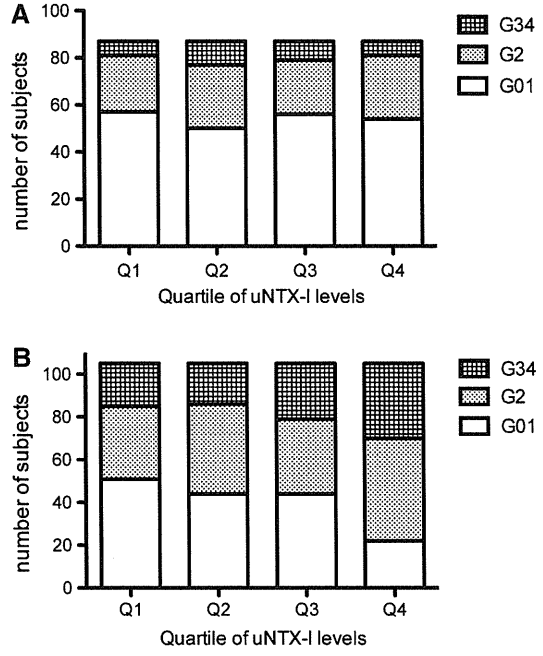

Fig. 5 The uNTX-I level and distribution of OA grades in 60–79 year-old **a** male and **b** female subjects. The mean values of uNTX-I (nmol BCE/mmol Cr) for each quartile from Q1–4 were 17.4, 28.0, 39.3, and 62.1 in males, and 20.7, 36.2, 50.5, and 75.4 in females. **a** n.s. and **b** $p = 0.0015$ 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

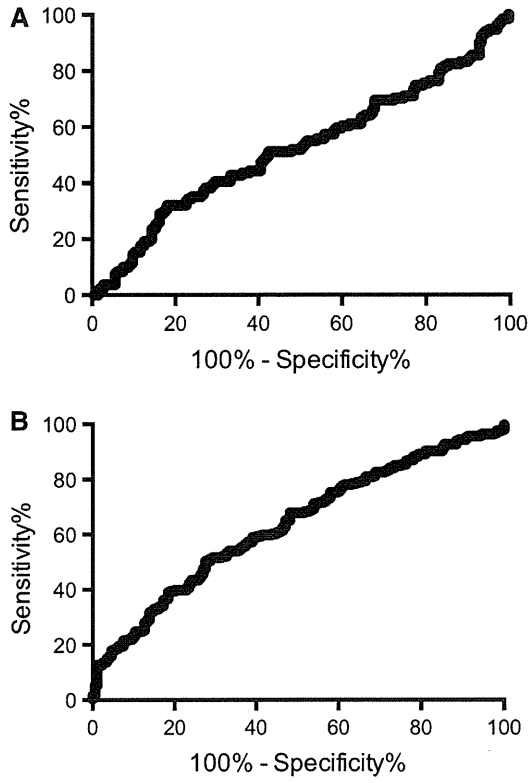

Fig. 6 ROC curve identifying the sensitivity and 100-specificity (%) of the measurement of the uCTX-II levels in men (**a**) and women (**b**) over 60 years of age. The area under the curve was 0.5229 ($p = 0.47$) and 0.6321 ($p < 0.0001$) in men and women, respectively

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.

Acknowledgments We express our gratitude to all of the people involved in the Matsudai district resident health check, and to all the residents who consented to participate in the study and provided samples. We also wish to thank SRL, Inc., (Tokyo, Japan) for their cooperation in collecting the samples and performing the measurements, and the staff of Niigata Medical Center Hospital, Niigata Institute of Health and Sports Medicine, and Niigata University of Health and Welfare for their cooperation in conducting the knee examinations. This work was supported by a Grant-in-Aid for Scientific Research B (19390389) and C (40377164).

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

References

1. Rousseau JCh, Garnero P. Biological markers in osteoarthritis. Bone. 2012;51:265–77.
2. Garnero P, Landewé R, Boers M, Verhoeven A, Van Der Linden S, Christgau S, Van Der Heijde D, Boonen A, Geusens P. Association of baseline levels of markers of bone and cartilage degradation with long-tern progression of joint damage in patients with early rheumatoid arthritis. The COBRA study. Arthritis Rheum. 2002;46:2847–56.
3. Landewé R, Geusens P, Boers M, van der Heijde D, Lems W, Koppele J, van der Linden S, Garnero P. Markers for type II collagen breakdown predict the effect of disease-modifying treatment on long-term radiographic progression in patients with rheumatoid arthritis. Arthritis Rheum. 2004;50:1390–9.
4. Garnero P, Conrozier T, Christgau S, Mathieu P, Delmas PD, Vignon E. Urinary type II collagen C-telopeptide levels are increased in patients with rapidly destructive hip osteoarthritis. Ann Rheum Dis. 2003;62:939–43.
5. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. Ann Rheum Dis. 2001;60:619–26.
6. Jordan KM, Syddall HE, Garnero P, Gineyts E, Dennison EM, Sayer AA, Delmas PD, Cooper C, Arden NK. Urinary CTX-II and glucosyl-galactosyl-pyridinoline are associated with the presence and severity of radiographic knee osteoarthritis in men. Ann Rheum Dis. 2006;65:871–7.
7. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J, Rodan GA, le Duong T. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum. 2004;50:1193–206.
8. Shiozaki H, Koga Y, Omori G, Yamamoto G, Takahashi HE. Epidemiology of osteoarthritis of the knee in a rural Japanese population. Knee. 1999;6:183–8.
9. Shiozaki H, Koga Y, Omori G, Tamaki M. Obesity and osteoarthritis of the knee in women; results of Matsudai Knee Osteoarthritis Survey. Knee. 1999;6:189–92.
10. Tanishi N, Yamagiwa H, Hayami T, Mera H, Koga Y, Omori G, Endo N. Relationship between radiological knee osteoarthritis and biochemical markers of cartilage and bone degradation (urine CTX-II and NTX-I): the Matsudai Knee Osteoarthritis Survey. J Bone Miner Metab. 2009;27:605–12.
11. Mouritzen U, Christgau S, Lehmann HJ, Tankó LB, Christiansen C. Cartilage turnover assessed with a newly developed assay measuring collagen type II degradation products: influence of age, sex, menopause, hormone replacement therapy, and body mass index. Ann Rheum Dis. 2003;62:332–6.
12. Lehmann HJ, Mouritzen U, Christgau S, Cloos PA, Christiansen C. Effect of bisphosphonates on cartilage turnover assessed with a newly developed assay for collagen type II degradation products. Ann Rheum Dis. 2002;61:530–3.
13. Sone T, Miyake M, Takeda N, Fukunaga M. Urinary excretion of type I collagen crosslinked N-telopeptides in healthy Japanese adults: age- and sex-related changes and reference limits. Bone. 1995;17:335–9.
14. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, Heinegård D, Jordan JM, Kepler TB, Lane NE, Saxne T, Tyree B, Kraus VB, Osteoarthritis Biomarkers Network. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage. 2006;14:723–7.

15. Sowers MF, Karvonen-Gutierrez CA, Yosef M, Jannausch M, Jiang Y, Garnero P, Jacobson J. Longitudinal changes of serum COMP and urinary CTX-II predict X-ray defined knee osteoarthritis severity and stiffness in women. Osteoarthritis Cartilage. 2009;17:1609–14.

16. Kong SY, Stabler TV, Criscione LG, Elliott AL, Jordan JM, Kraus VB. Diurnal variation of serum and urine biomarkers in patients with radiographic knee osteoarthritis. Arthritis Rheum. 2006;54:2496–504.

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2013; Early Online: 1–4
© 2013 Japan College of Rheumatology
DOI: 10.3109/14397595.2013.866921

informa
healthcare

ORIGINAL ARTICLE

Osteoporosis, vertebral fractures and mortality in a Japanese rural community

Akinobu Nishimura[1,2], Koji Akeda[1], Ko Kato[2], Kunihiro Asanuma[1], Tomomi Yamada[3], Atsumasa Uchida[1], and Akihiro Sudo[1]

[1]*Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Mie, Japan,* [2]*Department of Orthopaedics and Sports Medicine, Mie University Graduate School of Medicine, Mie, Japan, and* [3]*Department of Translational Medical Science, Mie University Graduate School of Medicine, Mie, Japan*

Abstract

Objectives. The present study aims to determine the relationship between osteoporosis (OP), vertebral fracture (VF) and mortality.
Methods. We followed up 1024 residents of Miyagawa village every 2 years for a mean of 8.4 years between 1997 and 2009. The residents were assessed every 2 years. We defined OP as T scores for bone mineral density that were <2.5 standard deviations below peak bone mass. VF was assessed by lateral radiography of the thoracic and lumbar spine. The participants were allocated as follows depending on the presence or absence of OP and VF: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group). We determined survival/mortality rates until 2011 by reviewing medical histories and death certificates.
Results. By 2011, 304 participants had died. The respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. Mortality rates were significantly worse for the OP + VF group than the Control group (OP + VF Hazard Ratio: 1.89; 95% CI, 1.27–2.77).
Conclusion. Prevention of osteoporotic VF in elderly persons is very important from the viewpoint of increasing life expectancy.

Keywords

Elderly, Epidemiology, Mortality, Osteoporosis, Vertebral fractures

History

Received 21 August 2013
Accepted 15 November 2013
Published online 23 December 2013

Introduction

Osteoporosis (OP) is characterized by increased bone loss and enhanced bone fragility. Japanese society is rapidly aging. Yoshimura et al. [1] described that about 6.4 and 11 million individuals in Japan have L2–4 and femoral neck OP. Therefore, OP and osteoporotic fractures are major public health problems in this aging society.

Vertebral fractures (VF) are the most common type of osteoporotic fracture, with an estimated annual incidence of 700 000 in the US [2] and 1.4 million in Europe [3]. Elderly persons typically develop VF due to bone fragility caused by OP. However, VF are sometimes caused by high-velocity accidents, such as car crashes or falls from a considerable height. Morphological evaluation by radiography alone cannot easily differentiate whether or not VF result from high-velocity accidents involving osteoporotic bone. However, the possibility that a combination of OP and VF causes osteoporotic VF might be quite high.

Some investigators have reported that low bone mineral density (BMD) is a risk factor for death [4,5]. If OP is independently associated with mortality, increased mortality might be associated with other types of osteoporotic fractures. Many studies have shown that osteoporotic [6–9], particularly hip [10–13], fractures are associated with increased mortality. Several recent studies of VF have also found that mortality is higher in patients with OP than in the general population [6,14–16]. However, Cummings and Melton [17] noted that most VF are subclinical or remain unrecognized without radiographic examination. Haczynski and Jakimiuk [16] also noted only one third of all VF are diagnosed clinically. Many studies have evaluated clinical (symptomatic) VF, but few have described mortality rates based on prevalent, radiographically defined VF [18,19].

We tested the hypothesis that osteoporotic, radiographic VF is associated with an increased risk of death among Japanese community dwellers.

Materials and methods

This population-based study of the residents of Miyagawa, a rural mountain village located in the center of Mie Prefecture, Japan, began in 1997. The participants were self-recruited, community-dwelling volunteers aged ≥ 65 years, who were assessed every 2 years from 1997 to 2011 at Houtoku Hospital for a total of eight studies. The population of the village in 1997 and 2010 was 4196 and 3490, respectively, when 1463 and 1553 residents, respectively, met the age criterion. This study proceeded at a local hospital, so participants had to arrive by public transportation or by other means, and they also had to understand the purpose of the study. Thus, the participants were generally healthier than non-participants.

Of 1271 residents (806 women and 465 men) who participated in these studies at least once, 1024 (661 women and 363 men) who

Correspondence to: Akinobu Nishimura, MD, PhD, Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan. Tel: +81-59-231-5022. Fax: +81-59-231-5211. E-mail: meiten@clin.medic.mie-u.ac.jp