In the MP-design, the ECP of the medial compartment located on the posterior edge of the ball-in-socket structure greater than 120° of flexion from bicondylar femoral rollback under the PCL-retained condition. Li et al.[21] evaluated the in vivo tibiofemoral contact kinematics of a cruciate-retaining TKA and showed that the current component design did not allow the femoral condyle to roll off the polyethylene edge at high degrees of flexion because of the geometry at the posterior lip. Abnormal contact conditions between the polyethylene insert and metal tray in the MP-design may present some risk of polyethylene wear or limitations of knee flexion. On the other hand, the lateral ECP of the DH-design showed paradoxical anterior translation from 0° to 60° knee flexion under the PCL-sacrificing condition, possibly because of the lesser conformity of the medial ball-in-socket structure by decreasing the height of the anterior and posterior lip. Recently, short- to mid-term clinical results of the Advance Medial Pivot prosthesis were reported. However, none of the authors clearly described the treatment for the PCL.[11,12,22] From the results of the present biomechanical study, it is recommended that the PCL should be sacrificed when the MP-design is used and retained when the DH-design is used.

There are several limitations because this is an in vitro cadaveric study. The first limitation is the number of specimens. Only seven cadaveric knees were evaluated in this study because it was difficult to obtain enough cadavers. Moreover, we selected knee joints of the same size for sequential evaluations, eliminating interspecimen variations. The second limitation is the loading condition. The load ratio of quadriceps and hamstring was close to physiological conditions; however, the actual amount of load was smaller than that of physiological condition as a result of the strength of the motion frame and load cell. In the near future, an in vivo kinematic study comparing the MP-design and the DH-design is needed.

The results of this study indicate that the ball-in-socket geometry in the MP-design has an advantage in reproducing medial pivot motion in the PCL-sacrificing condition and that the flexion path structure in the DH-design is effective for femoral rollback in the PCL-retaining condition. However, neither design is sufficient to reproduce medial pivot motion and posterior femoral rollback. Thus, a different design of tibial insert with a new concept is needed for more physiological kinematics after TKA.

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References

1. Walker PS, Hakek JV. The load-bearing area in the knee joint. J Biomech 1972;5:581–9.
2. Iwaki H, Pinskerova V, Freeman MAR. Tibiofemoral movement 1: the shapes and relative movements of the femur and tibia in the unloaded cadaver knee. J Bone Joint Surg 2000;82B: 1189–95.
3. Komistek RD, Dennis DA, Mahfouz M. In vivo fluoroscopic analysis of the normal human knee. Clin Orthop Relat Res 2003; 410:69–81.
4. Nakagawa S, Kadoya Y, Todo S, Kobayashi A, Sakamoto H, Freeman MAR, Yamano Y. Tibiofemoral movement 3: full flexion in the living knee studied by MRI. J Bone Joint Surg 2000;82B:1199–200.
5. Andriacchi TP, Galante JO, Fermier RW. The influence of total knee replacement design on walking and stair climbing. J Bone Joint Surg 1982;64A:1328–35.
6. Laskin RS. Joint line position restoration during revision total knee replacement. Clin Orthop Relat Res 2002;404:169–71.
7. Banks SA, Markovich GD, Hodge WA. In vivo kinematics of cruciate-retaining and -substituting knee arthroplasties. J Arthroplasty 1997;12:297–303.
8. Uvehammer J, Karrholm J, Brandsson S, Herberts P, Carlsson L, Regner L. In vivo kinematics of total knee arthroplasty: flat compared with concave tibial joint surface. J Orthop Res 2000; 18:856–64.
9. Stiehl JB, Komistek RD, Dennis DA, Paxson RD, Horff WA. Fluoroscopic analysis of kinematics after posterior-cruciate-retaining knee arthroplasty. J Bone Joint Surg 1995;77B:884–9.
10. Dennis DA, Komistek RD, Colwell CE, Ranawat CS, Scott RD, Thornhill TS, Lapp MA. In vivo anteroposterior femoro-tibial translation of the total knee arthroplasty: a multicenter analysis. Clin Orthop Relat Res 1998;356:47–57.
11. Blaha JD. A medial pivot geometry. Orthopedics 2002;25:963–4.
12. Schmidt R, Komistek RD, Blaha JD, Penenberg BL, Maloney WJ. Fluoroscopic analysis of cruciate-retaining and medial pivot knee implants. Clin Orthop Relat Res 2003;410:139–47.
13. Li G, DeFrate LE, Zayontz S, Park SE, Gill TJ. The effect of tibiofemoral joint kinematics on patellofemoral contact pressures under simulated muscle loads. J Orthop Res 2004;22:801–6.
14. Gill TJ, DeFrate LE, Wang C, Carey CT, Zayontz S, Zarins B, Li G. The effect of posterior cruciate ligament reconstruction on patellofemoral contact pressures in the knee joint under simulated muscle loads. Am J Sports Med 2004;32:109–15.
15. Hayashi T, Kurokawa M, Miyasaka M, Aizawa A, Kanaki A, Saito A, Ishioka A. A high-resolution line sensor-based photostereometric system for measuring jaw movements in 6 d.o.f. Front Med Biol Eng 1994;6:171–86.
16. Nishino K, Hayashi T, Suzuki Y, Koga Y, Omori G. Accuracy verification of the photostereometric system KKN/1B developed for intraoperative measurement of knee movement immediately after total knee arthroplasty. Front Med Biol Eng 1999;9: 261–73.
17. Omori G, Nishino K, Suzuki Y, Segawa H, Hayashi T, Koga Y. Intraoperative measurement of knee motion in total knee arthroplasty. Knee 2003;10:75–9.
18. Saari T, Uvehanmmer J, Carisson LV, Herberts P, Regnér L, Kärrholm J. Kinematics of three variations of the Freeman-Samuelson total knee prosthesis. Clin Orthop Relat Res 2003;410: 235–47.
19. Moonot P, Mu S, Railton GT, Field RE, Banks SA. Tibiofemoral kinematic analysis of knee flexion for a medial pivot knee. Knee Surg Sports Traumatol Arthrosc 2009;17:927–34.
20. Most E, Zayontz S, Li G, Otterberg E, Sabbag K, Rubash HE. Femoral rollback after cruciate-retaining and stabilizing total knee arthroplasty. Clin Orthop Relat Res 2003;410:101–13.

21. Li G, Suggs J, Hanson G, Durbhakula S, Johnson T, Freiberg A. Three-dimensional tibiofemoral articular contact kinematics of a cruciate-retaining total knee arthroplasty. J Bone Joint Surg 2006;88A:395–402.

22. Shakespeare D, Ledger M, Kinzel V. Flexion after total knee replacement. A comparison between the Medial Pivot knee and a posterior stabilized implant. Knee 2006;13:371–3.

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Short communication

Automated image registration for assessing three-dimensional alignment of entire lower extremity and implant position using bi-plane radiography

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ABSTRACT

An automated image-matching technique is presented to assess alignment of the entire lower extremity for normal and implanted knees and the positioning of implants with respect to bone. Sawbone femur and tibia and femoral and tibial components of a total knee arthroplasty system were used. Three spherical markers were attached to each sawbone and each component to define the local coordinate system. Outlines of the three-dimensional (3D) bone models and component computer-aided design (CAD) models were projected onto extracted contours of the femur, tibia, and implants in frontal and oblique X-ray images. Three-dimensional position of each model was recovered by minimizing the difference between the projected outline and the contour. Median values of the absolute error in estimating relative positions were within 0.5 mm and 0.6° for the femur with respect to the tibia, 0.5 mm and 0.5° for the femoral component with respect to the tibial component, 0.6 mm and 0.6° for the femoral component with respect to the femur, and 0.5 mm and 0.4° for the tibial component with respect to the tibia, indicating significant improvements when compared to manually obtained results.

1. Introduction

Progression of osteoarthritis of the knee is related to alignment of the lower extremity. Postoperative lower extremity alignment is commonly considered an important factor in determining favorable kinematics to achieve success in total knee arthroplasty (TKA) (Singerman et al., 1995). In addition, implant position with reference to bone is a critical factor affecting the long-term survival of TKA (Ritter et al., 1994).

Lower extremity alignment is currently assessed on a two-dimensional (2D) anteroposterior radiograph (Saleh et al., 1991; Sabharwal and Zhao, 2008) and may be influenced by position of the radiation source and orientation of the pelvis and lower extremity of the subject. Few studies have described the three-dimensional (3D) characteristics of lower extremity alignment during weight bearing (standing) (Cooke et al., 1994).

We have already developed a 3D lower extremity alignment assessment system with the subject in the standing position for pre-operative planning and postoperative alignment assessment for TKA (Sato et al., 2004, 2007). This system evaluates 3D alignment by manually matching projections of 3D bone and component models with images of the entire lower extremity on frontal and oblique X-ray images, but is time-consuming and lowers the accuracy of position estimation. Automation of the image-matching process is thus desirable to reduce the burden of this laborious task and improve the accuracy of position estimation.

The purpose of the present study was to present an automated image-matching technique for assessing alignment of the entire lower extremity for normal and implanted knees and for assessing implant positioning with respect to bone. Examination of the accuracy of position estimation is also presented.

2. Materials and methods

Sawbone femur and tibia and femoral and tibial components of the Advance total knee system (Wright Medical Technology, Arlington, TN, USA) were used. Three spherical acrylic markers (diameter, 25 mm) were attached to the femur and tibia and three spherical stainless markers (diameter, 5 mm) were attached to femoral and tibial components. Computed tomography (CT) was performed for the femur and tibia with these markers to reconstruct 3D surface models. Local coordinate systems of femoral and tibial surface models were defined based on central coordinates of markers attached to the surface models using a coordinate system creator (ModelViewer, LEXI, Tokyo, Japan). For components, computer-aided design (CAD) models were provided by the manufacturer. Using a 3D model editor (Magics 11, Materialise, Leuven, Belgium), 5 mm diameter spheres were placed at the actual positions of the markers measured by a 3D coordinate

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measuring machine (BH504, Mitutoyo, Kawasaki, Japan) with an accuracy of 1.0 μm. This machine measures 3D coordinates of the subject using a probe. A local coordinate system for each CAD model was then defined based on the central coordinates of the sphere models.

Four relative positions were obtained between femur and tibia, femoral component and tibial component, femoral component and femur, and tibial component and tibia. The femur and tibia were securely fixed at full extension using an external fixation device (Fig. 1A). The 3D position for each sawbone was determined based on central coordinates of the markers measured using the 3D coordinate measuring machine. Both femur and tibia were removed from the fixation device after biplanar X-ray exposure, which is described later, and femoral and tibial components were installed (Fig. 1B and C). The 3D position of each pair of bone and component was measured using the 3D coordinate measuring machine and biplanar X-ray images were taken. Each component was then removed and placed in a different position than before, and biplanar X-ray images were again taken. This process was performed a total of 4 times. The implanted femur and tibia were fixed again using the external fixation device (Fig. 1D). The 3D position measurement of each bone and biplanar X-ray exposure were performed on three different relative positions between the femur and tibia. Both components were then removed from both bones and fixed using a custom device (Fig. 1E). The 3D position measurement and biplanar X-ray exposure were performed on four relative positions between the two components. This separate measurement was performed due to the difficulty in touching the markers attached to the components with the probe when the implanted femur and tibia were fixed as shown in Fig. 1D. Note that one of the four relative positions between the femur and tibia was obtained before femoral and tibial components were installed.

A biplanar computed radiography system was used to capture frontal and oblique X-ray images. The rotation table was positioned at 0° and 60° relative to the optical axis of the X-ray source (Fig. 2). For each table position, X-ray tube calibration was performed beforehand to determine the projection matrix (Faugeras, 1993). The projection matrix provides 3D positioning of the focus of the X-ray source, and the image plane with respect to the calibration frame, enabling projections of 3D objects to be replicated on the image plane following X-ray exposure (Fig. 3). Contours of the femur, tibia and implants in biplanar radiographs were detected using the method described by Canny (1986). Projected outline points of each 3D model were the finite edge points of the 2D shadow created from the projections of all visible triangular surfaces of the 3D model.

For the ith point of the object contour, $\mathbf{p}_i$, the closest point of the projected outline of the corresponding model, $\mathbf{q}_i$, was examined. Distance between the two points was summed over all object contour points and subsequently normalized by the total number of points, N. Object function F represents the sum of normalized distances determined from frontal and oblique images:

$$F = \sum_{i=1}^{N^{FR}} |\mathbf{p}_i^{FR} - \mathbf{q}_i^{FR}|/N^{FR} + \sum_{i=1}^{N^{OB}} |\mathbf{p}_i^{OB} - \mathbf{q}_i^{OB}|/N^{OB}, \quad (1)$$

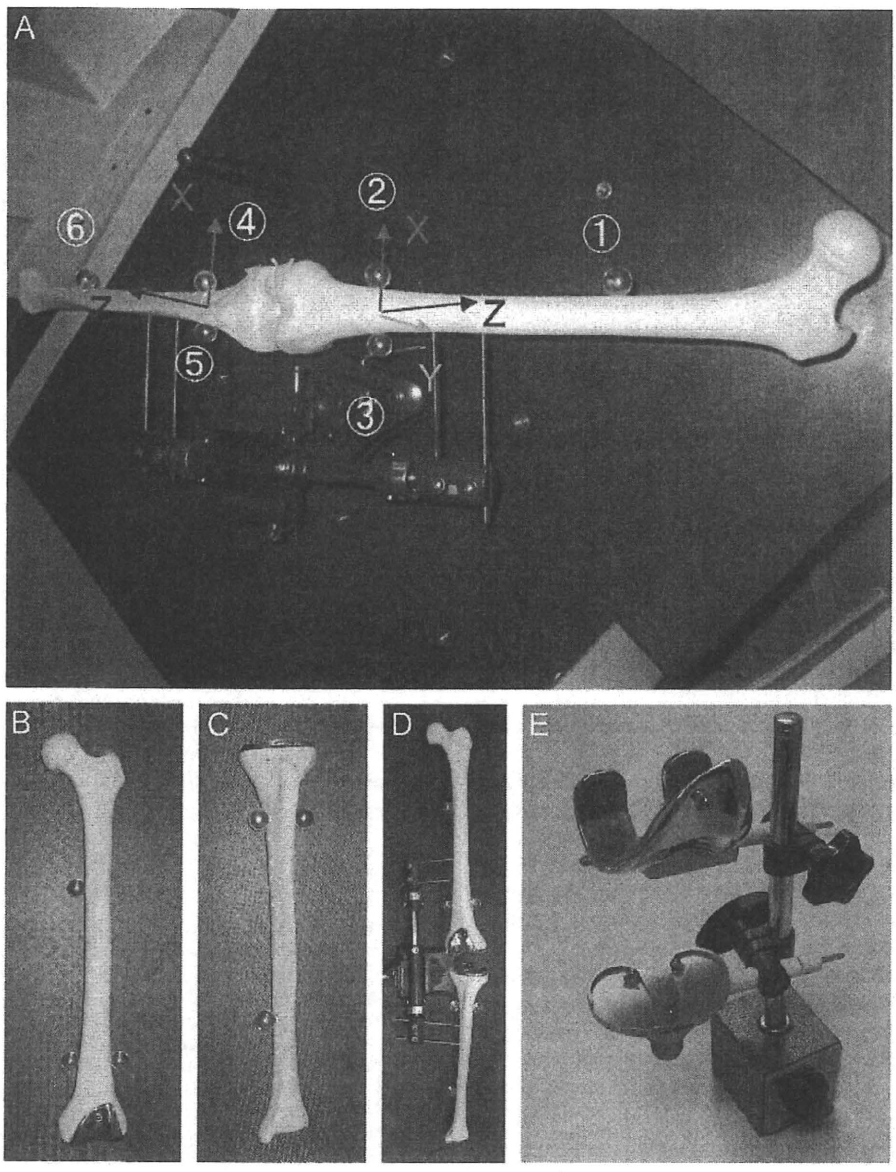

Fig. 1. Set-up for measurement of relative position. (A) The sawbone femur and tibia were immobilized using an external fixation device. (B) Femur with the femoral component attached. (C) Tibia with tibial component attached. (D) The implanted femur and tibia were immobilized using an external fixation device. (E) Femoral and tibial components were immobilized using a custom fixation device.

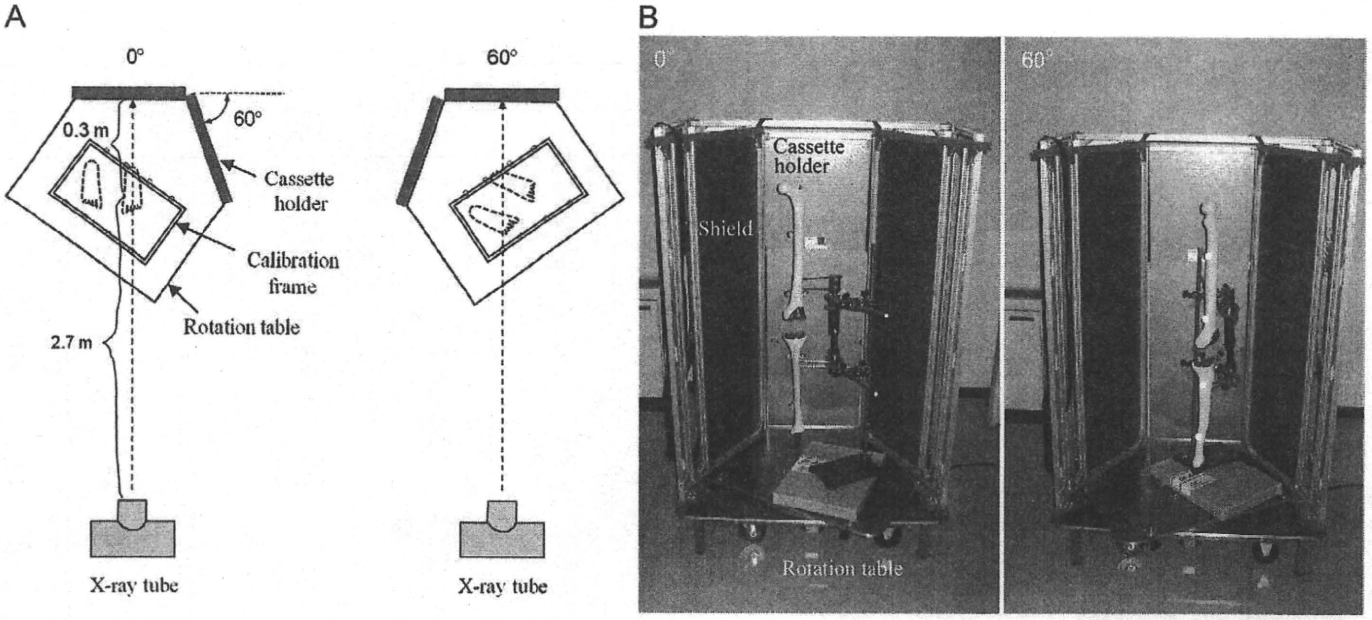

Fig. 2. Calibration set-up for the rotation table for bi-plane radiography (A). An acrylic frame with 72 spherical stainless markers attached was used for calibration. Half of the 72 markers were attached to the frontal surface, and the other half attached to the back surface to cover the volume of the lower extremity ($270 \times 180 \times 800\,mm^3$). The 3D positions of these markers were measured using the 3D coordinate measuring machine. The two cassettes rotated with the table, while normal directions were set to align with the optical axis. Each cassettes contained three $14 \times 14\,in^2$ imaging plates that were to be digitized in 8-bit gray intensity with 0.2 mm resolution (FCR; Fuji, Tokyo, Japan). Diameters of markers were 4 mm for frontal surface markers and 3 mm for back surface markers. This discrepancy was used to emphasize differences in projected size of the marker in radiographs, to facilitate identification of markers. Footprints indicate the standing position of the subject, where the left leg is being imaged. The repeatability (standard deviation) of table positioning between the table positioned at 0° and 60° was ±0.3° (n=5). Fixed femur and tibia were X-rayed at 0° and 60° (B).

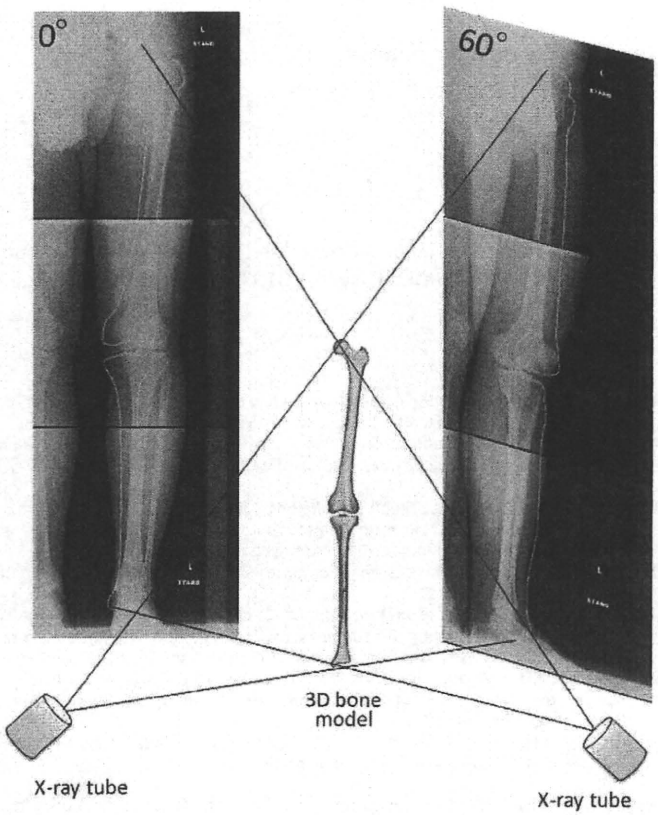

Fig. 3. Synthetic biplanar X-ray system. Projected outline points of each 3D model were the finite edge points of the 2D shadow created from the projections of all visible triangular surfaces of the 3D model.

where superscripts *FR* and *OB* denote the values standing for frontal and oblique images. The 3D position of each model (full 6-degrees of freedom (DOF) parameters) was recovered by minimizing F using the downhill simplex algorithm (Nelder and Mead, 1965). Ten sets of initial 6-DOF parameters for minimization were arbitrarily chosen from ±5.0° and ±5.0 mm of true values of each relative position. The minimization procedure terminates if either the number of iterations exceeds 500 or the relative change in F is below 0.00005. Manual image matching was also performed from 10 sets of initial 6-DOF parameters arbitrarily ranging within ±5.0° and ±5.0 mm of true values.

3. Results

Mean values, standard deviations, and median values of absolute errors in relative position parameters determined by manual and automated methods are listed in Table 1. The automated method produced significantly better results for all position parameters, except for rotation about the x-axis and translation along the x-axis at the relative position of the femoral component with respect to the femur (The Wilcoxon signed-rank test). The running times for automated minimization on a Windows XP PC (XEON processor, 3 GHz, 2 GB RAM) of about 270 s for bone and 30 s for components were reduced from those for the manual method (about 600 s for bone and 300 s for components).

4. Discussion

Image-based techniques for direct 3D measurements of bone and implant positions are a practical approach, since the insertion of markers into bone is not required. Our automated method offered better accuracy and time efficiency than the manual method. However, the present results were less accurate than those obtained by de Bruin et al. (2008) and Li et al. (2004),

Table 1
Mean, SD, and median value of absolute error for estimating 6-DOF parameters of relative positions (n=40).

Relative position			Rotation			Translation		
			x (°)	y (°)	z (°)	x (mm)	y (mm)	z (mm)
Femur/tibia	Manual	Mean	0.6	0.5	1.5	1.0	1.6	1.1
		SD	0.4	0.4	1.0	0.8	1.4	0.9
		Median	0.4	0.4	1.3	0.8	1.4	0.9
	Automated	Mean	0.2	0.3	0.7	0.3	0.5	0.5
		SD	0.2	0.2	0.4	0.3	0.3	0.2
		Median	0.1	0.3	0.6	0.1	0.5	0.5
		p	<0.001	0.005	0.001	<0.001	<0.001	<0.001
Femoral component/tibial component	Manual	Mean	0.8	0.9	1.0	1.1	0.6	1.1
		SD	0.7	0.5	0.7	0.7	0.4	0.7
		Median	0.6	1.0	0.9	1.1	0.6	1.0
	Automated	Mean	0.3	0.4	0.4	0.5	0.3	0.5
		SD	0.2	0.3	0.3	0.4	0.2	0.3
		Median	0.3	0.3	0.5	0.4	0.4	0.5
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Femoral component/femur	Manual	Mean	0.7	1.2	1.0	0.9	1.7	1.2
		SD	0.4	0.7	0.8	0.8	0.9	1.0
		Median	0.6	0.4	0.5	0.6	0.5	0.3
	Automated	Mean	0.6	0.5	0.5	0.7	0.6	0.5
		SD	0.3	0.3	0.3	0.4	0.5	0.4
		Median	0.6	0.4	0.5	0.6	0.5	0.3
		p	0.170	<0.001	0.011	0.687	<0.001	0.001
Tibial component/tibia	Manual	Mean	0.5	1.8	0.6	0.9	1.3	1.0
		SD	0.3	1.0	0.4	0.6	1.1	0.8
		Median	0.5	1.9	0.5	0.7	1.1	0.8
	Automated	Mean	0.2	0.6	0.4	0.3	0.4	0.5
		SD	0.2	0.5	0.2	0.2	0.3	0.3
		Median	0.1	0.4	0.4	0.3	0.4	0.5
		p	<0.001	<0.001	0.042	<0.001	<0.001	0.001

p-Values indicate significance of the difference between automatically obtained results and manually obtained results.

probably due to small differences in positions of the rotation table and cassette holder from those set during camera calibration. Conversely, our results for the standard deviation of estimating implant position in reference to bone were equivalent to that determined using postoperative CT (Jazrawi et al., 2000).

Cooke et al. (1994) provided quantitative lower limb alignment parameters in the coronal and sagittal planes using anteroposterior and lateral radiographs taken using a turntable, but did not quantify the axial parameters because the axial geometry of the lower extremity was not reconstructed in three dimensions. The present method would therefore enable more reliable analysis of load-bearing characteristics across the knee joint.

The use of CT may lower the applicability of our method, due to concerns about exposure to radiation. However, although the effective radiation dose of 6 mSv from CT is about 10 times larger than that required for radiography, this dose is comparable to the annual effective dose from natural background radiation of about 3 mSv (Mettler et al., 2008). Although magnetic resonance imaging can be regarded as an alternative method, imaging the entire length of the femur or tibia is currently difficult. The choice of CT is thus relevant for the purposes of this method.

When applying this method to patients, care must be taken to prevent body motion during X-ray exposure. In addition, since the soft tissues surrounding bone may reduce the reliability of contour extraction from bone, studies examining actual patients are needed to clarify the clinical applicability of this procedure.

In conclusion, the present study demonstrates the accuracy of relative 3D position estimation using an automated image-matching technique in experiments with bi-plane radiographs of sawbones and TKA components.

Conflict of interest statement

None.

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References

Canny, A., 1986. A computational approach to edge detection. IEEE Transactions on Pattern Analysis and Machine Intelligence PAMI 8 (6), 679–698.
Cooke, T.D.V., Li, J., Scudamore, R.A., 1994. Radiographic assessment of bony contributions to knee deformity. Orthopedic Clinics of North America 25 (3), 387–393.
de Bruin, P.W., Kaptein, B.L., Stoel, B.C., Reiber, J.H.C., Rozing, P.M., Valstar, E.R., 2008. Image-based RSA: Roentgen stereophotogrammetric analysis based on 2D–3D image registration. Journal of Biomechanics 41, 155–164.
Faugeras, O., 1993. Three-Dimensional Computer Vision: A Geometric Viewpoint. MIT Press, Cambridge.
Jazrawi, L.M., Birdzell, L., Kummer, F.J., Di Cesare, P.E., 2000. The accuracy of computed tomography for determining femoral and tibial total knee arthroplasty component rotation. Journal of Arthroplasty 15 (6), 761–766.
Li, G., Wuerz, T.H., DeFrate, L.E., 2004. Feasibility of using orthogonal fluoroscopic images to measure in vivo joint kinematics. Journal of Biomechanical Engineering 126, 314–318.
Mettler, F.A., Huda, W., Yoshizumi, T.T., Mahesh, M., 2008. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 248 (1), 254–263.
Nelder, J.A., Mead, R., 1965. A simplex method for function minimization. Computer Journal 7, 308–313.
Ritter, M.A., Faris, P.M., Keating, E.M., Meding, J.B., 1994. Postoperative alignment of total knee replacement. Its effect on survival. Clinical Orthopaedics and Related Research 299, 153–156.

Sabharwal, S., Zhao, C., 2008. Assessment of lower limb alignment: supine fluoroscopy compared with a standing full-length radiograph. Journal of Bone and Joint Surgery (American) 90, 43–51.

Saleh, M., Harriman, P., Edwards, D.J., 1991. A radiological method for producing precise limb alignment. Journal of Bone and Joint Surgery (British) 73, 515–516.

Sato, T., Koga, Y., Omori, G., 2004. Three-dimensional lower extremity alignment assessment system. Application to evaluation of component position after total knee arthroplasty. Journal of Arthroplasty 19 (5), 620–628.

Sato, T., Koga, Y., Sobue, T., Omori, G., Tanabe, Y., Sakamoto, M., 2007. Quantitative 3-dimensional analysis of preoperative and postoperative joint lines in total knee arthroplasty. Journal of Arthroplasty 22 (4), 560–568.

Singerman, R., Heiple, K.G., Davy, D.T., Goldberg, V.M., 1995. Effect of tibial component position on patella strain following total knee arthroplasty. Journal of Arthroplasty 10 (5), 651–656.

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ORIGINAL ARTICLE

Pulmonary Function Analysis of Japanese Athletes: Possibly Even More Asthmatics in the Field

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ABSTRACT

Background: The prevalence of bronchial asthma (BA) in youth is increasing in Japan, but very few athletes are reported to be affected with BA. The aim of this study is to analyze pulmonary function test (PFT) in athletes from the aspect of BA retrospectively.

Methods: Medical history questionnaires of 2111 athletes (male: 1549, female: 562) were reviewed. All athletes participated in the institute's athletic test for the first time, from April 2003 through March 2006. Athletes were categorized into three groups; current-BA confirmed and treated by the physician, possible-BA according to the allergic history and/or BA symptoms, and non-BA that is neither of the above two groups. The PFT data were then analyzed.

Results: There were 24 current-BA (1.1%), 137 possible-BA (6.5%), and 183 cases with a past history of BA (PH; 8.7%). Percent of predicted forced expiratory volume in 1 second (%FEV_1) and of predicted peak expiratory flow rate (%PEF) in current-BA (86.2 ± 17.7% and 81.6 ± 19.1%, respectively) and possible-BA (84.7 ± 14.6% and 81.2 ± 17.3%, respectively) were significantly lower than those in non-BA (93.9 ± 13.7% and 93.8 ± 19.8%, respectively), without any significant difference between current-BA and possible-BA. Athletes with PH show impaired obstructive indices; even in non-BA with PH showed lower %FEV_1 (91.3 ± 13.9%, $p < 0.05$) and %PEF (86.8 ± 17.8%, $p < 0.001$) than non-BA without PH (94.0 ± 13.7% and 94.2 ± 19.9%, respectively).

Conclusions: The incidence of BA in Japanese athletes may be higher than currently recognized. More intervention is encouraged for the diagnosis of BA, to avoid any fatal asthma during sports by initiating preventive therapy.

KEY WORDS

asthma, athletic injuries, exercise-induced asthma, exercise-induced bronchospasm, pulmonary function test

INTRODUCTION

A negligible number of Japanese athletes requested the use of an inhaled beta agonist (IBA) at recent Olympic Games[1]; only one out of 268 athletes from Japan applied for permission at the Sydney Games, where 112 out of 594 athletes from the United States of America notified the use. This low prevalence of notification by Japanese athletes may be partly due to the relatively low prevalence of bronchial asthma (BA) patients in Japan.

The prevalence of BA among Japanese children has increased by 3% in the last 20 years, and two recently conducted government surveillances have revealed the rate in school-age children to be 5.7 and 7.6%. In 2003, the Global Initiative for Asthma (GINA) also reported a similar rate of 6.7% as the prevalence of BA symptoms in Japanese school-age children,

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Authors' contributions: TH, ES and MA made conception and design of this paper. MH, GO, and FG performed the administrative support. MH and MA provided the study materials or patients. JT, TH and MH contributed to collection and assembly of data. JT, TH and TK performed the data analysis and interpretation. JT and TH wrote the manuscript. All the authors have read and approved the final manuscript.

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Table 1 Medical questionnaire regarding history and symptoms of bronchial asthma and allergy

BA † history:
1. Is the athlete on the follow-up of BA at the clinic? (current-BA)
2. Has the athlete been diagnosed as BA during the childhood? (PH ‡)
BA symptoms:
3. Has the athlete ever been diagnosed as allergic disease other than BA?
4. Has any of the family (siblings or parents) been diagnosed as BA?
5. Does the athlete experience wheezing, chest tightness, breathlessness, cough, or excess of sputum at night or early in the morning?
6. Does the athlete experience wheezing, chest tightness, breathlessness, cough, or excess of sputum after exposure to the certain airborne substances (allergens or pollutants)?
7. Does the athlete experience wheezing, chest tightness, breathlessness, cough, or excess of sputum during and after the exercise?
8. Does the athlete experience wheezing, chest tightness, breathlessness, cough, or excess of sputum as the seasonal exacerbation?
9. Do the athlete' s colds take more than 14 days to clear up? (One point for each "yes" answer to question 3 through 9, and the athlete is considered possible-BA if the score is three or greater.)

† BA, bronchial asthma.

‡ PH, past history of asthma.

which is below the rate for the United States of America, 10.9%.[2]

The prevalence of BA in athletes is higher than in the general population,[3-7] and considering the difference in prevalence between Japan and the United States of America shown above, many Japanese athletes possibly have undiagnosed BA; the percentage of Japanese athletes who applied for the use of IBA is too low referring to the prevalence of BA among Japanese children. Moreover, there is no published report so far, regarding the prevalence of asthma-related disorders among Japanese athletes.

Thus, we have decided to analyze the baseline pulmonary function test (PFT) data regarding the BA background of athletes, since our medical questionnaire for the health check-ups included the BA-related history and symptoms. Recent studies show that the medical questionnaires or interviews are not reliable in identifying the exercise-induced bronchospasm (EIB).[8] EIB should be documented by evaluating the PFT in response to appropriate exercise or provocation tests. However, medical history is still a helpful guide in the clinical diagnosis of BA, and can be used in screening of BA regardless of EIB.

The primary aim of this study was to analyze screening PFT of Japanese athletes from the aspect of BA, by the groups categorized through the scoring of a medical questionnaire regarding asthma symptoms and allergic history.

METHODS

STUDY DESIGN

We conducted a cross-sectional retrospective study of regional elite athletes who participated in their first athletic test performed at the Niigata Institute for Health and Sports Medicine, from April 2003 through March 2006. A total of 2111 athletes (1549 males, 562 females, age 18.0 ± 4.1 years) were included in this study. The data from screening tests were collected during the preparticipation health check-ups, including a medical questionnaire focused on history and symptoms of BA and allergy (Table 1), and baseline PFT. The study procedures including participant's anonymity preservation were approved by the Ethical Committee of the Niigata Institute for Health and Sports Medicine in accordance with the principles embodied in the Declaration of Helsinki, and each subject, parents, or legal guardian provided written informed consent.

ASTHMA AND ALLERGY QUESTIONNAIRE

A detailed BA and allergy history and review of symptoms were obtained using a medical questionnaire as shown in Table 1. The questionnaire consisted of 9 items relevant to the diagnosis of BA, also referring to the medical history consideration shown by GINA,[9] and an athlete was categorized as current-BA, possible-BA, or non-BA. The athlete was considered current-BA if BA was confirmed and treated by the physician, possible-BA if scoring 3 or more items for the allergic history and/or BA symptoms, and non-BA if the athlete was neither current-BA nor possible-BA. Possible-BA, however, was defined as above in this study to categorize athletes into groups, simply for the sake of convenience to analyze baseline PFT retrospectively.

PULMONARY FUNCTION TEST BY SPIROMETRY

A baseline PFT by spirometry was performed for all participants. The best value from three measurements of vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second

Table 2 Categorical characteristics of the participants

	Number (%)	Male/Female
Total participants	2111 (100)	1549/562
Current-BA	24 (1.1)	17/7
(PH^+	20	15/5)
Possible-BA	137 (6.5)	97/40
(PH^+	48	40/8)
Non-BA	1950 (92.4)	1435/515
(PH^+	115	80/35)

(FEV_1), peak expiratory flow (PEF) were used and recorded by a spirometer, SpiroSift SP-470 (Fukuda Denshi, Tokyo, Japan.). Predicted values were calculated by the standard formulae originally programmed in the spirometer.

DATA ANALYSIS AND STATISTICS

Percent of predicted FEV_1 (%FEV_1), percent of predicted PEF (%PEF), and FEV_1/FVC (FEV_1%) were analyzed for each category of athletes, current-BA, possible-BA, and non-BA. The data were further analyzed according to the past history of asthma (PH) status. Values for all measurements are expressed as mean (%) ± SD.

Kruskal-Wallis test, and Mann-Whitney *U* tests were used to determine the levels of difference between all groups. Significance was assumed at *p*-values of <0.05.

RESULTS

There were 24 current-BA (1.1%), 137 possible-BA (6.5%), and 1950 non-BA (92.4%) cases. In 183 cases of PH (8.7%), there were 20 current-BA, 47 possible-BA, and 116 non-BA cases. Considering the rate of PH, cumulative morbidity of BA was estimated as 8.9%. The difference between male and female athletes was not discussed in this study, because 562 female athletes were analyzed, and there were only seven cases with current-BA and 40 cases with possible-BA, which resulted in numbers that were too few to see any significance (Table 2).

As shown in Figure 1, current-BA showed a significantly decreased %FEV_1 (current-BA vs. non-BA; 86.2 ± 17.7% vs. 93.9 ± 13.7%), %PEF (81.6 ± 19.1% vs. 94.3 ± 26.2%) and FEV_1% (84.6 ± 8.3% vs. 89.0 ± 5.8%) compared to non-BA, even under the relevant treatment ($p < 0.001$). Interestingly, possible-BA is also significantly decreased in pulmonary function parameters compared to non-BA (possible-BA vs. non-BA; 84.7 ± 14.6% vs. 93.9 ± 13.7% in %FEV_1, 81.2 ± 17.3% vs. 94.3 ± 26.2% in %PEF, and 84.9 ± 7.5% vs. 89.0 ± 5.8% in FEV_1%, all with $p < 0.001$, respectively). However, there was no significant difference between current-BA and possible-BA (Fig. 1). %VC, which is one of restrictive indices in PFT, was of no difference among all groups (data not shown).

To determine the influence of PH on pulmonary function, comparison between groups either with or without PH was performed. Among all participants, the group with PH (PH^+) showed decreased pulmonary function parameters compared to the group without PH (PH^-) (PH^+ vs. PH^-; 89.9 ± 14.3% vs. 93.5 ± 14.0% in %FEV_1, $p < 0.001$. 87.2 ± 17.8% vs. 93.4 ± 20.0% in %PEF, $p < 0.005$. 86.8 ± 6.6% vs. 88.8 ± 6.0% in FEV_1%, $p < 0.001$.). In regard to non-BA, PH^+ also revealed decreased airway function compared to PH^- (PH^+ vs. PH^-; 91.3 ± 13.9% vs. 94.0 ± 13.7% in %FEV_1, $p < 0.05$. 86.8 ± 17.8% vs. 94.2 ± 19.9% in %PEF, $p < 0.001$. 87.3 ± 6.0% vs. 89.1 ± 5.8% in FEV_1%, $p < 0.005$.). In contrast, when the samples are limited to possible-BA, the findings were vice versa; PH^- had decreased airway function in comparison with PH^+ (PH^+ vs. PH^-; 87.6 ± 13.1% vs. 83.2 ± 15.2% in %FEV_1, $p = 0.104$. 89.0 ± 17.6% vs. 77.1 ± 15.7% in %PEF, $p < 0.005$. 86.8 ± 6.8% vs. 84.0 ± 7.7% in FEV_1%, $p < 0.05$.). And even in 24 current-BA, though sample numbers were too small to make conclusions, PH^- in this category had a tendency for decreased airway function compared to PH^+ except for FEV1% (PH^+ vs. PH^-; 87.0 ± 18.5% vs. 81.6 ± 14.4% in %FEV_1. 84.2 ± 19.5% vs. 67.3 ± 10.8% in %PEF. 84.5 ± 8.5% vs. 85.1 ± 7.8% in FEV_1%.) (Table 3).

DISCUSSION

The study by Hammerman, *et al.* showed that there were 5.7% BA or EIB among American high school athletes, and another 6.1% were identified as having undiagnosed BA.[10] In the present study, although the athletes defined as possible-BA were not medically confirmed as BA at the time of visit, the obstructive indices of PFT showed similar results compared with current-BA. These data suggest that a considerable number of these athletes may also have undiagnosed BA.

A recent nation-wide survey on the health and welfare status by the Japanese government revealed that 71.3% of the all-age patients with BA symptoms were under antiasthmatic medication, but only 54.6% of such patients aged between 15 and 34 years were under relevant treatment.[11] Of 161 athletes with either current-BA or possible-PA in our study, less than 15% of them were current-BA who were on medication, thus indicating that the prevalence of untreated BA may also be higher among athletes. Importantly, a 7-year observation of BA deaths by Becker, *et al.* report that of 61 casualties during sport activities, 55 cases had mild intermittent or persistent BA before their fatal attack, and that only 3 of them used long-term controller medication.[12] Although most of the non-current-BA athletes tested in our study had little respiratory symptoms during and after the usual exercise, the undiagnosed BA should thoroughly be detected, in order to avoid any future BA deaths related to exercise and sport activities.

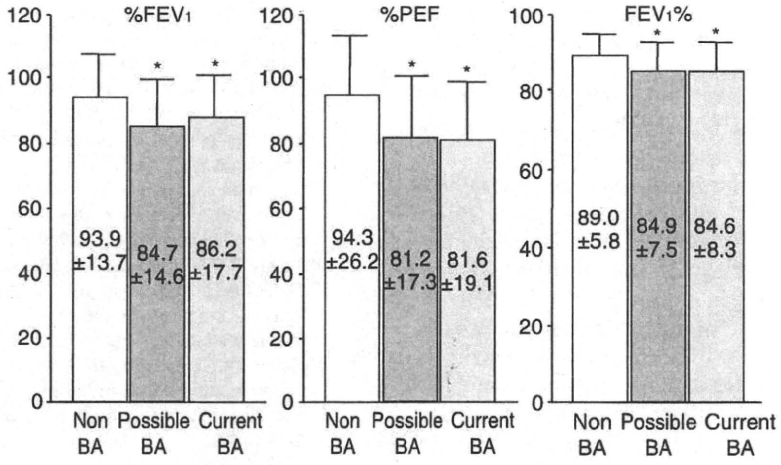

Fig. 1 Obstructive indices of pulmonary function tests (%FEV_1, %PEF, and FEV_1%) in athletes. Data express mean (%) ± SD. * $p < 0.001$ by the Kruskal-Wallis test.

Table 3 Obstructive indices of pulmonary function test in athletes with or without past history of asthma.

	%FEV_1 (%)	%PEF (%)	FEV_1% (%)
All participants			
PH^+ ($n = 183$)	89.9 ± 14.3***	87.2 ± 17.8**	86.8 ± 6.6***
PH^- ($n = 1928$)	93.5 ± 14.0	93.4 ± 20.0	88.8 ± 6.0
Current-BA			
PH^+ ($n = 20$)	87.0 ± 18.5†	84.2 ± 19.5†	84.5 ± 8.5†
PH^- ($n = 4$)	81.6 ± 14.4	67.3 ± 10.8	85.1 ± 7.8
Possible-BA			
PH^+ ($n = 48$)	87.6 ± 13.1	89.0 ± 17.6**	86.8 ± 6.8*
PH^- ($n = 89$)	83.2 ± 15.2	77.1 ± 15.7	84.0 ± 7.7
Non-BA			
PH^+ ($n = 115$)	91.3 ± 13.9*	86.8 ± 17.8***	87.3 ± 6.0**
PH^- ($n = 1835$)	94.0 ± 13.7	94.2 ± 19.9	89.1 ± 5.8

Data express mean ± SD, *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$; compared with PH^-.

† Insufficient sample numbers for statistical analysis.

Another important message is derived from the results concerning the influence of PH on pulmonary function. The present study has shown that athletes with PH, who were even considered as non-BA, had impaired pulmonary function indices, suggesting they may not have fully recovered from their childhood asthma. In general, it has been reported that up to 70% of BA patients in childhood lose their symptoms during puberty.[13,14] Osward, *et al.* conducted 28-year follow-up study for mild asthmatics in childhood, and suggested that airway obstruction or hyperresponsiveness of the patients would be restored normally even if they did not use inhaled corticosteroids.[15] On the contrary, Agertoft, *et al.* showed that a delay in the introduction of inhaled corticosteroids resulted in incomplete recovery of pulmonary function.[16] Moreover, Pederson, *et al.* reported that early intervention with sufficient doses of inhaled corticosteroids could cure the disease with no recurrence.[17] In this regard, our data may also indicate the possible insufficiency of the treatment approach to childhood BA leading to the symptom takeover through the youth generation, and we should be careful with PH^+ in non-BA patients who have little BA symptoms. Another valuable finding regarding the effect of PH status is that PH^- in possible-BA had decreased airway function compared with PH^+. This tendency is also observed in current-BA (Table 3). Although the details in the treatment history of BA is limited in the medical record, it is more likely that PH^+ in these categories received treatment intervention in the past, which may apparently improve the respiratory function, assuming possible-BA has high potential for being true BA.[18]

We included questionnaires of respiratory symptoms and PFT at baseline medical check-ups, with the belief that these findings are important in the clinical diagnosis of BA. However, they may be insufficient for the diagnosis of EIB. Rundell, *et al.* found that among elite athletes, a diagnosis based on self-reported symptoms is no more accurate than a coin toss. In that study, 61% of EIB-positive athletes reported symptoms, and 45% of normal pulmonary function athletes reported symptoms of EIB.[19] Methacholine challenge test is often used for BA/EIB diagnosis in Japan, but it should be noted that a relatively low sensitivity for EIB diagnosis especially in summer sports is reported for this provocation.[20] We have recently started additional bronchial challenge tests such as eucapnic voluntary hyperpnea and hypertonic saline inhalation, together with exercise challenge which are the current challenge tests also recommended by the International Olympic Committee for the diagnosis of BA/EIB in athletes.

In summary, the PFT results at the Niigata Institute for Health and Sports Medicine were analyzed, according to the historical background of BA, and the prevalence of current-BA, possible-BA, and the cumulative morbidity of BA among the regional elite athletes were 1.1, 6.5, and 8.9%, respectively. A limitation of this study is in the retrospective analysis using a medical questionnaire, of which data had been adopted from sufficient but non-uniform medical record formats. The effectiveness of this medical questionnaire in the uniform medical record format on scoring should be confirmed, and is currently under prospective investigation.

Finally, considering the epidemiological data on BA in athletes available so far, the incidence of BA among the Japanese athletes may be higher than currently recognized. More intervention is encouraged for diagnosing BA and related subtypes to avoid any fatal asthma attacks during sport activities, and to restore originally expected athletic performance of the affected individuals.

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REFERENCES

1. Fitch KD. Beta2-Agonists at the Olympic Games. *Clin Rev Allergy Immunol* 2006;**31**:259-68.
2. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469-78.
3. Larsson K, Ohlsen P, Larsson L, Malmberg P, Rydstrom PO, Ulriksen H. High prevalence of asthma in cross country skiers. *BMJ* 1993;**307**:1326-9.
4. Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. *J Allergy Clin Immunol* 1998;**102**:722-6.
5. Weiler JM, Ryan EJ 3rd. Asthma in United States olympic athletes who participated in the 1998 olympic winter games. *J Allergy Clin Immunol* 2000;**106**:267-71.
6. Chowgule RV, Shetye VM, Parmar JR *et al.* Prevalence of respiratory symptoms, bronchial hyperreactivity, and asthma in a megacity. Results of the European community respiratory health survey in Mumbai (Bombay). *Am J Respir Crit Care Med* 1998;**158**:547-54.
7. Turcotte H, Langdeau JB, Thibault G, Boulet LP. Prevalence of respiratory symptoms in an athlete population. *Respir Med* 2003;**97**:955-63.
8. Hallstrand TS, Curtis JR, Koepsell TD *et al.* Effectiveness of screening examinations to detect unrecognized exercise-induced bronchoconstriction. *J Pediatr* 2002; **141**:343-8.
9. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Available at: http://www.ginasthma.co./GuidelinesResources.asp?l1=2&l2=0. Accessed April 30, 2009.
10. Hammerman SI, Becker JM, Rogers J, Quedenfeld TC, D'Alonzo GE Jr. Asthma screening of high school athletes: identifying the undiagnosed and poorly controlled. *Ann Allergy Asthma Immunol* 2002;**88**:380-4.
11. The Ministry of Health, Labour and Welfare of Japan. [Health and welfare survey on allergic symptoms in 2003]. Available at: http://wwwdbtk.mhlw.go.jp/toukei/data/230/2003/toukeihyou/0004683/t0099341/Table12_001.html (in Japanese). Accessed January 10, 2009.
12. Becker JM, Rogers J, Rossini G, Mirchandani H, D'Alonzo GE Jr. Asthma deaths during sports: report of a 7-year experience. *J Allergy Clin Immunol* 2004;**113**:264-7.
13. Nicolai T, Illi S, von Mutius E. Effect of dampness at home in childhood on bronchial hyperreactivity in adolescence. *Thorax* 1998;**53**:1035-40.
14. Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;**61**:642-6.
15. Oswald H, Phelan PD, Lanigan A *et al.* Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997; **23**:14-20.
16. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;**88**:373-81.
17. Pedersen S. Can steroids cause asthma to remit? *Am J Respir Crit Care Med* 1996;**153**:S31-2.
18. Kauppinen R, Sintonen H, Vilkka V, Tukiainen H. Long-term (3-year) economic evaluation of intensive patient education for self-management during the first year in new asthmatics. *Respir Med* 1999;**93**:283-9.
19. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. *Med Sci Sports Exerc* 2001;**33**:208-13.
20. Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: Challenges for diagnosis. *J Allergy Clin Immunol* 2002;**110**:374-80.

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ORIGINAL ARTICLE

Relationship between radiological knee osteoarthritis and biochemical markers of cartilage and bone degradation (urine CTX-II and NTX-I): the Matsudai Knee Osteoarthritis Survey

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Abstract Biochemical markers of cartilage and bone degradation are becoming increasingly important in the evaluation of knee osteoarthritis (OA). To clarify the correlation between radiological knee OA and urine CTX-II (C-terminal crosslinking telopeptide of collagen type II) or urine NTX-I (N-terminal crosslinking telopeptide of type I collagen), we conducted a cross-sectional study in the cohorts of the epidemiological knee survey at the Matsudai district in Niigata Prefecture, Japan. Urine specimens were collected from 296 subjects, and CTX-II and NTX-I were measured using ELISA. Standing knee AP X-rays were obtained and graded according to the Kellgren–Lawrence classification. The subjects were then divided by gender, age (40- to 59-year-old group and 60- to 79-year-old group), and the X-ray grade (Grade 0, 1, Grade 2, and Grade 3, 4). In non-OA (Grade 0, 1) subjects, the 60- to 79-year-old group had significantly higher CTX-II values than the younger group only in females. The subjects of both genders aged over 60 years of age with OA Grade 3, 4 had significantly higher CTX-II values than the Grade 0, 1 group or the Grade 2 group. For NTX-I, there were no significant differences between each OA grade although the Grade 3, 4 group females from 60 to 79 years of age had higher values than the Grade 2 group. In addition, in the 60- to 79-year-old subjects of both genders, a positive correlation was observed between the urine CTX-II and urine NTX-I. For the subjects ranging from 60 to 79 years of age in both genders, the urine CTX-II values indicate the progression of OA. In addition, the weak but positive correlation between urine CTX-II and urine NTX-I in the subjects ranging from 60 to 79 years of age in both genders suggests that bone resorption and cartilage degradation appear to develop in parallel.

Keywords Knee osteoarthritis · Urine CTX-II · Urine NTX-I

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Introduction

In the last several years, the average age of people in Japan has been increasing rapidly, and knee osteoarthritis (OA) is becoming a very frequently occurring disease. Currently, diagnosis of knee OA is based on symptoms, history, physical findings, laboratory findings of the blood and synovial fluid, 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., the Knee Society Score, the Japanese Orthopaedic Association Knee OA score), and QOL assessments (e.g., SF-36, WOMAC

score, Japanese Osteoarthritis Measure score [1]). The findings of each examination and assessment are considered to mainly provide information of the current conditions of knee OA and therefore help to determine the optimal treatment method at that point. However, these findings 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 early diagnosing knee OA and predicting the degree of progression and prognosis. If useful joint biomarkers are found and can be applied clinically, they would be very beneficial in terms of both medicine and medical economics. Currently, joint biomarkers include substrate markers formed by degradation products of joint tissues such as pyridinoline [2] and cartilage oligomeric matrix protein (COMP) [3], enzymes that exist in the joints such as matrix metalloproteinases (MMPs) [4], tissue inhibitors of metalloproteinases (TIMPs) [5], interleukins [6], other inflammatory cytokines, or nitric oxide (NO) [7]. No definite joint biomarkers, however, have yet been found.

When type II collagen, which is the main component of joint cartilage, is degraded by a cartilage-degrading enzyme, C-terminal crosslinking telopeptide of collagen type II (CTX-II) is produced and excreted through urine. Garnero et al. [8, 9] have reported that the urine CTX-II value was significantly high in patients with early rheumatoid arthritis and that it could be used as an index for reaching diagnosis, thus predicting X-ray progression, and determining the effects of drug therapy. In addition, patients with hip OA exhibited higher values of urine CTX-II than healthy subjects, and cases of rapidly developing hip OA had significantly higher CTX-II values than cases of slowly developing hip OA [10]. Moreover, the urine CTX-II values of patients with developed radiological knee OA were higher [11, 12], thus indicating the possibility that CTX-II can be used joint biomarker that anticipates the progression of knee OA. There have been several reports regarding urine CTX-II, but there are few reports of urine CTX-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 females and share similar ages of onset, definite information has not yet been obtained. In recent reports, it has been experimentally revealed that subchondral bone resorption and subsequent bone sclerosis occurs in conjunction with the progression of knee OA [13]. 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 four epidemiological surveys on knee OA at intervals of 7 years during the 21 years from 1979 to 2000 in Matsudai district (formerly Matsudai-machi) in Tokamachi, Niigata Prefecture, Japan during which time resident health checks were conducted every year, and we have published a number of reports regarding the risk factors of knee OA [14, 15]. To provide the first step in verifying our hypothesis that urine CTX-II can be used as a joint biomarker for knee OA, we investigated the correlation between the knee OA X-ray grades obtained from the same cohorts and the urine CTX-II values as well as the urine NTX-I (N-terminal crosslinking telopeptide of type I collagen) values, which is a bone metabolism biomarker, while taking the age and gender of the subjects into consideration.

Subjects and methods

For the resident annual health check-up conducted in the Matsudai district in Tokamachi City, Niigata Prefecture in 2006, we mailed a letter requesting the cooperation of the residents who had been randomly selected in advance based on their resident registration code numbers, and we then collected urine specimens and took standing AP X-rays of their knees for 296 subjects from whom consent was obtained on the day of the health check. The study protocol was approved by the Ethical Committee of Niigata University Graduate School of Medical and Dental Sciences.

Blind X-ray assessments were conducted by the two senior authors (G. O. and Y. K.), in accordance with the Kellgren–Lawrence classification, and whenever there was a difference in grade between right and left, the higher grade was employed. As with the past reports, the grades 0 and 1 were defined as the non-OA group and grades 2 or more were defined as the OA group. Table 1 shows the X-ray grades of the knee OA of the cases, the number of the subjects, and their age distribution.

The urine specimens were stored at −80°C after being collected, CTX-II was measured using a Urine CartiLaps enzyme linked immunosorbent assay (ELISA) kit (Nordic

Table 1 Demographics of subject's age, gender, and X-ray grade of knee OA

Number of subjects	X-ray grade of knee OA			
	G 0, 1	G 2	G 3	G 4
Total	106	126	45	19
Age (years)[a]	60 ± 14.7	67.3 ± 9.3	73.1 ± 6.6	75.8 ± 5.6
Male	47	55	17	6
Age*	61.6 ± 15.5	69.4 ± 9.3	76.9 ± 6.0	74.7 ± 3.1
Female	59	71	28	13
Age	58.7 ± 14.0	65.7 ± 9.1	70.9 ± 6.0	76.4 ± 6.5

[a] Mean ± SD

Biosciences, Hevlev, Denmark), and NTX-I was measured using an Osteomark NTx ELISA kit (Inverness Medical Innovations, Princeton, NJ, USA). The measured values were corrected with urine creatinine (CTX-II: ng/mmol Cr, NTX-I: nmol BCE/mmol Cr).

For statistical analysis, we used the Mann–Whitney *U*-test, Kruskal Wallis *H*-test, and Spearman correlation test, all of which are nonparametric tests, and $P < 0.05$ was defined statistically significant. All values are shown to be the mean ± standard deviation as well as the median.

Results

Comparison of urine CTX-II by age

First, without considering the OA grades, the urine CTX-II values were compared between the two groups comprising 40- to 59-year old subjects and 60- to 79-year-old subjects, respectively, according to gender. In the male subjects, the average urine CTX-II value in the 40- to 59-year-old group ($n = 20$) was 206.2 ± 111.9 (mean ± SD) or 209.5(median) ng/mmol Cr and the average value in the 60- to 79-year-old group ($n = 83$) was 252.1 ± 129.0 or 213.5. There were no significant differences between the two groups. In the female subjects, the average urine CTX-II value in the 40- to 59-year-old group ($n = 30$) was 184.0 ± 72.4 or 164.4 ng/mmol Cr and the average value in the 60- to 79-year-old group ($n = 128$) was 305.0 ± 157.8 or 266.7. The urine CTX-II values in the 60- to 79-year-old group were significantly higher than those in the 40- to 59-year-old group (Fig. 1).

Comparison of urine CTX-II by age in the non-OA group

To eliminate the effects of OA grade, we limited the next comparisons to the non-OA group (G 0, 1) and compared the urine CTX-II values of the two groups comprising the 40- to 59-year-old subjects and the 60- to 79-year-old subjects, respectively, according to gender. In the male subjects, the average urine CTX-II value in the 40- to 59-year-old group ($n = 15$) was 223.8 ± 121.0 (mean ± SD) or 213.9 (median) ng/mmol Cr and the average value in the 60- to 79-year-old group ($n = 22$) was 209.4 ± 105.0 or 195.0. There were no significant differences between the two groups. In the female subjects, the average urine CTX-II value in the 40- to 59-year-old group ($n = 22$) was 175.3 ± 65.4 or 161.3 ng/mmol Cr and the urine average CTX-II value in the 60- to 79-year-old group ($n = 30$) was 270.0 ± 117.9 or 231.7. The urine CTX-II values in the 60- to 79-year-old group were significantly higher than those in the 40- to 59-year-old group (Fig. 2).

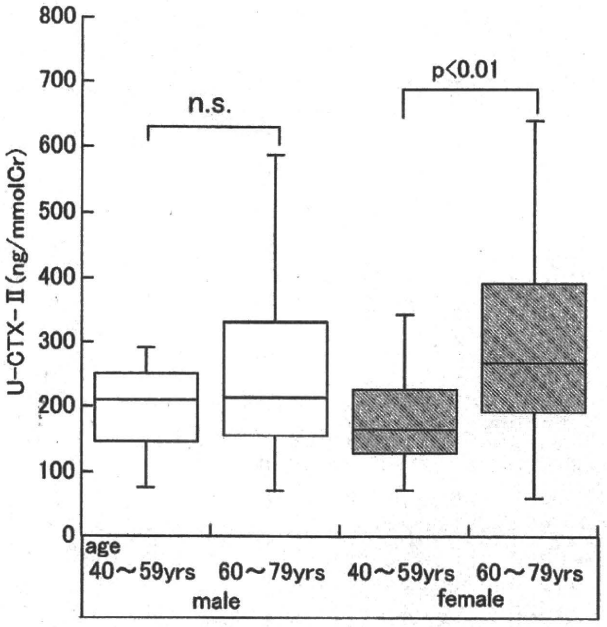

Fig. 1 Relationship between age (40–59:60–79 years) and the urinary CTX-II level in male and female subjects. Each *box* represents the 25th/50th (median) to 75th percentiles. The *lines outside the box* represent the 10th and 90th percentiles

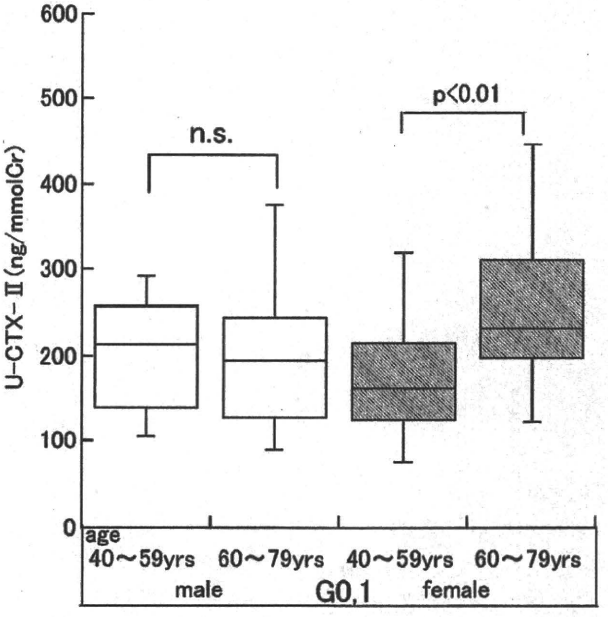

Fig. 2 Relationship between age (40–59:60–79 years) and the urinary CTX-II level in male and female subjects with knee X-ray OA Grade 0 and 1

Urine CTX-II values by X-ray OA grade

For all the male subjects regardless of age, the CTX-II values were compared among each of the following groups:

the Grade 0, 1 group ($n = 47$), the Grade 2 group ($n = 55$), and the Grade 3, 4 group ($n = 23$). The average values were: 208.1 ± 104.2 (mean ± SD) or 193.0 (median) ng/mmol Cr in the Grade 0, 1 group; 229.0 ± 118.2 or 204.7 in the Grade 2 group; and 336.9 ± 161.6 or 329.9 in the Grade 3, 4 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group. The Grade 3, 4 group had significantly higher urine CTX-II values than the Grade 0, 1 group and the Grade 2 group (Fig. 3).

Next, in the 40- to 59-year-old male subjects, the urine CTX-II values were compared between the Grade 0, 1 group ($n = 15$) and the Grade 2 group ($n = 5$) (there were no cases of grade 3 or 4). The values were 223.8 ± 121.0 or 213.9 in the Grade 0, 1 group and 153.3 ± 59.6 or 149.0 in the Grade 2 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group. In the 60- to 79-year-old male subjects, the CTX-II values were compared between each of the following groups: the Grade 0, 1 group ($n = 23$), the Grade 2 group ($n = 43$), and the Grade 3, 4 group ($n = 17$). The values were: 206.6 ± 103.4 or 193.0 in the Grade 0, 1 group; 246.2 ± 124.0 or 212.4 in the Grade 2 group; and 328.6 ± 143.5 or 330.0 in the Grade 3, 4 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group. The Grade 3, 4 group had significantly higher urine CTX-II values than the Grade 0, 1 group or the Grade 2 group. The mean age of each group was not significantly different (72.0 ± 4.3 in the Grade 0, 1, 70.0 ± 4.9 in the Grade 2, and 73.8 ± 3.9 in the Grade 3, 4).

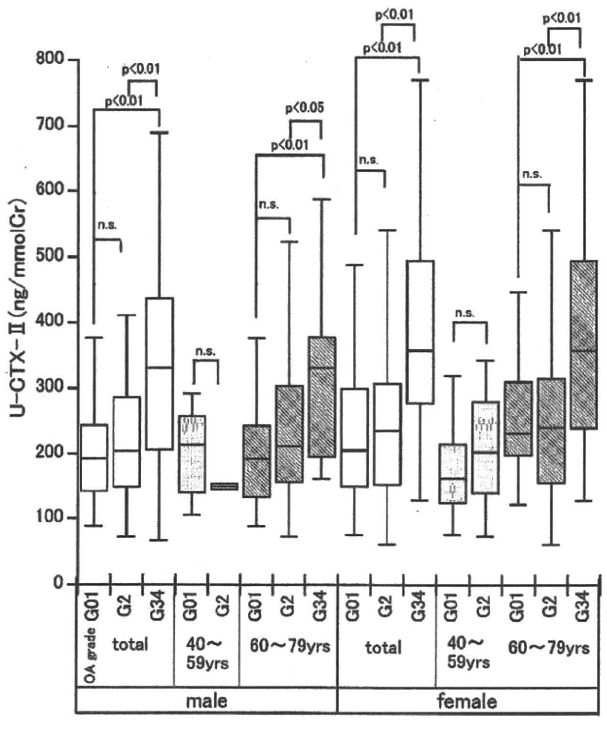

Fig. 3 Relationship between the knee X-ray OA grade and the urinary CTX-II level in male and female subjects. A statistical analysis was performed between different OA grade groups in each age group

For all the female subjects regardless of age, the CTX-II values were compared between each of the following groups: the Grade 0, 1 group ($n = 59$), the Grade 2 group ($n = 71$), and the Grade 3, 4 group ($n = 41$). The values were 230.0 ± 112.1 (mean ± SD) or 205.5 (median) ng/mmol Cr in the Grade 0, 1 group; 266.8 ± 150.8 or 234.9 in the Grade 2 group; and 385.3 ± 161.5 or 356.9 in the Grade 3, 4 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group, but the Grade 3, 4 group had significantly higher urine CTX-II values than both the Grade 0, 1 group and the Grade 2 group.

In the 40- to 59-year-old female subjects, the urine CTX-II values were compared between the Grade 0, 1 group ($n = 22$) and the Grade 2 group ($n = 8$) (there were no cases of grade 3 or 4). In the results, the values were 175.0 ± 65.4 or 161.3 in the Grade 0, 1 group and 207.3 ± 89.6 or 203.2 in the Grade 2 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group. In the 60- to 79-year-old female subjects, the CTX-II values were compared between each of the following groups: the Grade 0, 1 group ($n = 30$), the Grade 2 group ($n = 61$), and the Grade 3, 4 group ($n = 37$). The values were: 270.0 ± 117.9 or 231.7 in the Grade 0, 1 group; 274.8 ± 155.3 or 240.7 in the Grade 2 group; and 382.8 ± 166.2 or 356.9 in the Grade 3, 4 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group, but the Grade 3, 4 group had significantly higher urine CTX-II values than both the Grade 0, 1 group and the Grade 2 group. The mean age of each group was not significantly different (68.0 ± 5.5 in the Grade 0, 1, 68.6 ± 5.1 in the Grade 2, and 71.4 ± 5.6 in the Grade 3, 4).

Comparison of NTX-I by age in the non-OA group

To eliminate the effects of OA grade, the urine NTX-I values were compared between the two groups comprising the 40- to 59-year-old subjects and the 60- to 79-year-old subjects, respectively, in the non-OA group (Grade 0, 1) according to gender. The NTX-I values in the 40- to 59-year-old ($n = 15$) and 60- to 79-year-old ($n = 23$) males of Grade 0, 1 was 33.8 ± 14.7 (mean ± SD) or 29.2 (median) nmol BCE/mmol Cr and 33.6 ± 12.5 or 30.4, respectively. There were no significant differences between the two groups. The NTX-1 values in the 40- to 59-year-old ($n = 22$) and 60- to 79-year-old ($n = 30$) females of Grades 0 and 1 was 35.5 ± 14.7 or 34.7 and 55.2 ± 21.5 or 51.3, respectively. The urine NTX-I values in the 60- to 79-year-old group were significantly high (Fig. 4).

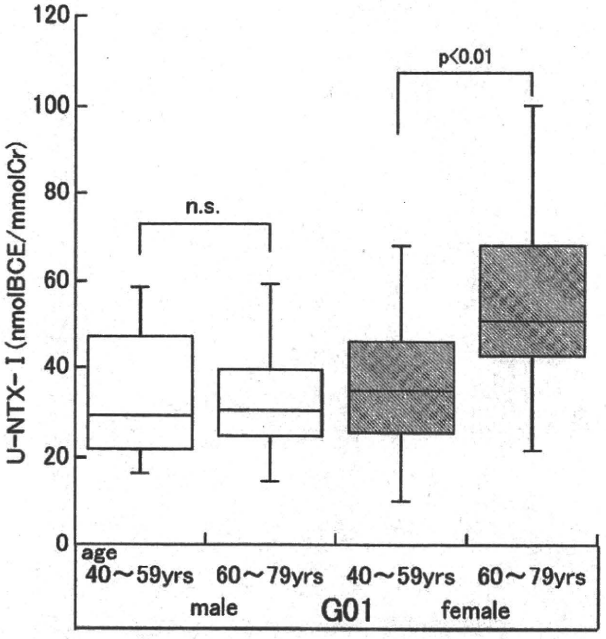

Fig. 4 Relationship between age (40–59:60–79 years) and the urinary NTX-I level in male and female subjects with knee X-ray OA Grade 0, 1

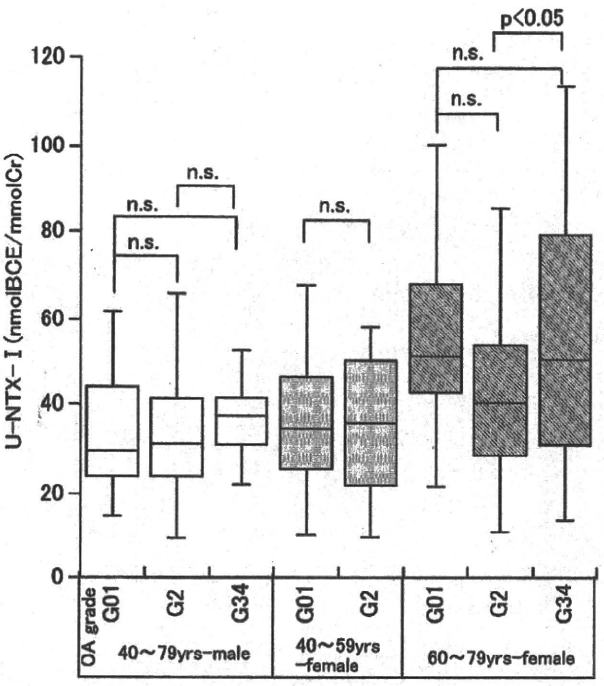

Fig. 5 Relationship between knee the X-ray OA grade and urinary the NTX-I level in male and female subjects

Comparison of the urine NTX-I based on the X-ray OA grade

Considering that the effects of age on the NTX-I values are small in male subjects, we used 40- to 79-year-old male subjects to compare the urine NTX-I values between the Grade 0, 1 group ($n = 38$), the Grade 2 group ($n = 48$), and the Grade 3, 4 group ($n = 17$). The average values were: 33.7 ± 13.2 (mean ± SD) or 29.8 (median) nmol BCE/mmol Cr in the Grade 0, 1 group; 33.7 ± 14.6 or 31.4 in the Grade 2 group; and 36.5 ± 11.8 or 37.5 in the Grade 3, 4 group. There were no significant differences between any of the groups (Fig. 5).

In the 40- to 59-year-old female subjects, the urine NTX-I values were compared between the Grade 0, 1 group ($n = 22$) and the Grade 2 group ($n = 8$) (there were no cases of Grade 3 or 4). The average values were 35.5 ± 14.7 or 34.7 in the Grade 0, 1 group and 35.6 ± 17.6 or 36.1 in the Grade 2 group. There were no significant differences between the two groups. In the 60- to 79-year-old female subjects, the urine NTX-I values were compared between each of the following groups: the Grade 0, 1 group ($n = 30$), the Grade 2 group ($n = 61$), and the Grade 3, 4 group ($n = 37$). The average values were: 55.3 ± 21.5 or 51.3 in the Grade 0, 1 group; 43.8 ± 19.9 or 40.6 in the Grade 2 group; and 56.2 ± 29.7 or 50.6 in the Grade 3, 4 group. There were no significant differences between the Grade 0, 1 group and the Grade 2 group or the Grade 3, 4 group, but the Grade 3, 4 group had significantly higher values than the Grade 2 group.

Relationship between the urine CTX-II and urine NTX-I

The correlation between urine the CTX-II and urine NTX-I levels in the 40- to 59-year-old male subjects ($n = 20$) showed a correlation coefficient of 0.28 and a P-value of 0.23, thus indicating no correlation to exist between the two (Fig. 6a). In the 60- to 79-year-old male subjects ($n = 83$), the correlation coefficient was 0.40 and the P-value was 8.14E-6, showing a significantly positive correlation (Fig. 6b).

In the 40- to 59-year-old female subjects ($n = 30$), the correlation coefficient was 0.33 and the P-value was 0.07, thus indicating no correlation to exist (Fig. 6c). In the 60- to 79-year-old female subjects ($n = 128$), the correlation coefficient was 0.47 and the P-value was 1.11E-8, showing a significantly positive correlation (Fig. 6d).

Discussion

Mouritzen et al. [16] have reported that, in terms of age, urine CTX-II peaks at the age of 20–25 years old in both gender before subsequently decreasing and slowly increasing again in conjunction with aging at the age of

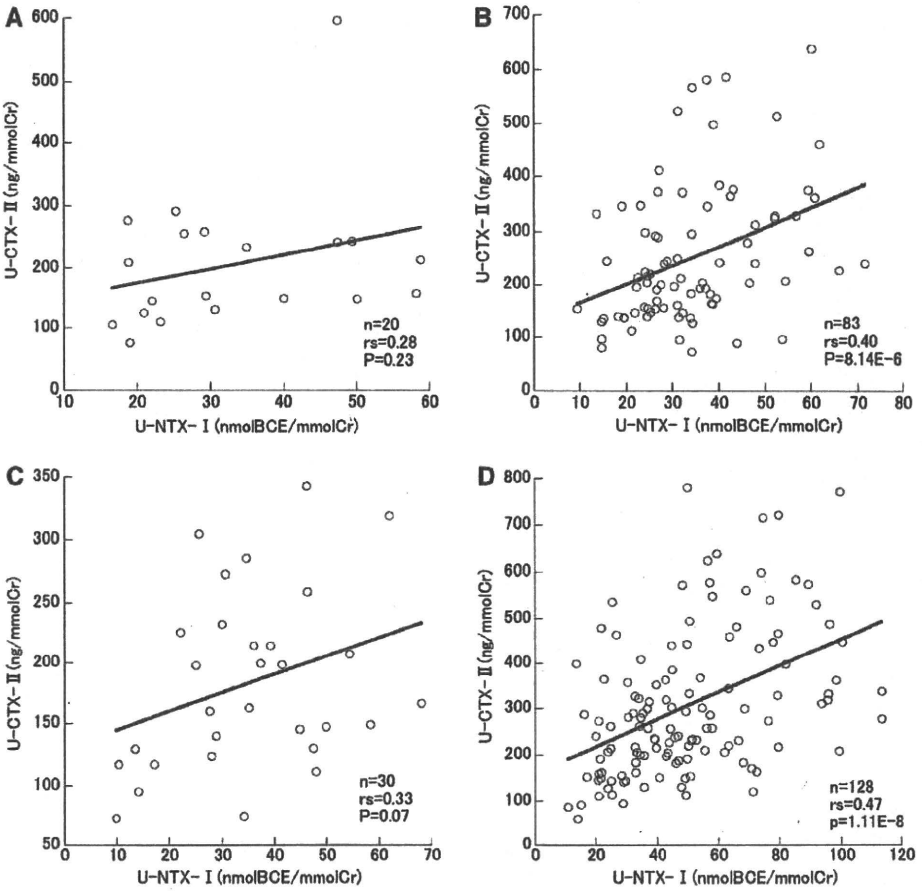

Fig. 6 Correlation between the urinary NTX-I level and the urinary CTX-II level in **a** male aged 40–59 years, **b** male aged 60–79 years, **c** female aged 40–59 years, and **d** female aged 60–79 years. Significant differences ($P < 0.05$) were observed only in 60–79 years of both genders

55 years or older. In addition, urine CTX-II values are significantly higher after menopause than before menopause [16]. Moreover, urine CTX-II values are significantly higher in subjects without hormone replacement therapy (HRT) than in subjects with HRT [16]. In addition, Lehmann, et al. [17] reported that urine CTX-II values in females after menopause decreased with the use of a bisphosphonate. In this study, taking age, gender, and X-ray OA grade into consideration, we proceeded with an examination of urine CTX-II and urine NTX-I as described below.

Relationship between age and urine CTX-II

We at first examined the changes in urine CTX-II by age. The number of cases in each group was set as carefully as possible to avoid any problems in conducting a statistical analysis, and the cases were divided into two groups: the 40- to 59-year-old group and the 60- to 79-year-old group.

In the male subjects, the 60- to 79-year-old group tended to exhibit higher values than the 40- to 59-year-old group, though there were no significant differences. In the female subjects, the 60- to 79-year-old group had significantly higher values than the 40- to 59-year-old group. Considering that menopause in Japanese females often occurs between the ages of 45 and 55 (average 50.5 years), almost all the subjects in the 60- to 79-year-old female group had experienced menopause. So, the 60- to 79-year-old group exhibited significantly higher values than the 40- to 59-year-old group because menopause had strongly affected the urine CTX-II values as reported by Mouritzen et al.

Relationship between X-ray OA grade and urine CTX-II

Using the X-ray OA grade as an index, we examined the changes in urine CTX-II value caused by the progression of OA. The number of cases in each group was set as carefully as possible to avoid problems in conducting a statistical analysis, and the cases were divided into three groups: the Grade 0, 1 group, the Grade 2 group, and the Grade 3, 4 group. We made comparisons between the OA grades of each gender while limiting the comparisons to 40- to 59-year-old subjects and 60- to 79-year-old subjects. The results showed that in the 40- to 59-year-old subjects, for both males and females, there were no significant

differences between different OA grades. However, no definitive conclusions could be made because this age group only includes the Grade 0, 1 group and the Grade 2 group, and the number of cases in the Grade 2 group is very small. In addition, it would be difficult for female subjects ranging 40–59 years of age to determine changes in knee OA from only a single measurement of urine CTX-II value because the value is affected by both age-specific change and the presence or absence of menopause.

In the 60- to 79-year-old subjects, for both males and females, there were no significant differences between the Grade 0, 1 group and the Grade 2 group, whereas the Grade 3, 4 group had significantly higher values than the Grade 0, 1 group and the Grade 2 group. This is consistent with the report by Garnero et al. [12] in which the urine CTX-II values in the X-ray OA grade progressive group are high, but their report only covers males in their 60s. Our study shows that the urine CTX-II values of cases of progressive knee OA are significantly high for cases at the age of 60 years or older, both for males and females.

In this study, in the 60- to 79-year-old male and female subjects, when comparing the knee OA Grade 0, 1 group and the Grade 2 group, the urine CTX-II values were slightly higher in the Grade 2 group than in the Grade 0, 1 group both for the mean value and the median value, but there were no significant differences. One of the possible causes of small difference may lie in the inconsistency of the X-ray grade judgment, but another reason is that the X-ray changes alone are not sufficient to elucidate the changes actually occurring on the articular surface. We often find that the fibrillation and ulceration of knee cartilage tend to be stronger than expected from preoperative X-ray findings in arthroscopic surgery. Such cases as those demonstrating an "impending grade 2", thus theoretically leading to an increase in the CTX-II value, are likely to be included in the Grade 1 group, thus affecting the results. The results of this study indicate the necessity to conduct time-lapse measurements of the joint biomarkers with repeat radiological examinations over a long-term course, especially for cases of early radiological OA.

Relationship between age and urine NTX-I

It has been reported that in males, urine NTX-I is almost constant throughout the ages of 20–79 years old without being affected by age [18]. In this study, no significant differences in the urine NTX-I value were observed between the two age groups of the non-knee OA (Grade 0, 1) male group. It is commonly known that in females, urine NTX-I values are strongly affected by age and particularly menopause. In this study, urine NTX-I values in the 60- to 79-year-old group, in which almost all the subjects had menopause, had increased significantly compared to the 40- to 59-year-old group as shown previously.

Relationship between urine CTX-II, urine NTX-I, and X-ray OA grade of knee

Previously, OA and osteoporosis were believed to be inversely correlated [19], and it has been reported that high bone mineral density (BMD) and BMD gain decreased the risk of progression of radiographic knee OA but may be associated with an increased risk of incident knee OA [20]. However, the relationship between the occurrence and development of OA and osteoporosis still remains unclear. In this study, there was no correlation between the urine CTX-II and urine NTX-I levels in the 40- to 59-year-old male and female subjects. However, in the 60- to 79-year-old male and female subjects, the urine CTX-II and urine NTX-I levels were weakly but positively correlated. This indicates that the urine CTX-II level, which is a cartilage degradation marker, increases in parallel with the increase in the urine NTX-I level, which is a bone resorption marker. Moreover, when the X-ray grade was taken into consideration, the urine CTX-II value of the 60- to 79-year-old male and female subjects was significantly higher in the Grade 3, 4 group than in either the Grade 0, 1 group and the Grade 2 group. For NTX-I value, we found significant difference between the Grade 2 group and the Grade 3, 4 group only in the 60- to 79-year-old female subjects although there was no significant difference between the Grade 0, 1 group and the Grade 3, 4 group. Bettica et al. [21] have longitudinally analyzed the Chingford Study and reported that in the 4-year follow-up of the radiological progressive OA group of females after menopause, urine NTX-I increased significantly compared to the non-progressive OA group, thus indicating that the progression of bone resorption is involved with the progression of OA. These findings suggest that there might be the weak but positive correlation between OA progression and bone resorption.

In conclusion, this study is the first report of the relationship between urine CTX-II and X-ray knee OA grade conducted using a Japanese common resident health check-up, taking age and gender into consideration. The results show that at the age of 60–79 years old, the Grade 3, 4 group had significantly higher urine CTX-II values than the Grade 0, 1 group and the Grade 2 group, indicating that increased urine CTX-II value at this age indicates the progression of knee OA. In addition, in this age range, we found that urine CTX-II and urine NTX-I were weakly but positively correlated, indicating that bone resorption and cartilage degradation are developing in parallel. This cross-sectional study indicates that urine CTX-II, which is a cartilage biomarker, is correlated with the radiological

knee OA grade within a certain age range and can be used as an evaluative method for OA. We will conduct the same type of study with larger number of cases to confirm our results and also long-term evaluations using clinical cases to determine whether the progression of OA can be predicted, which is the fundamental purpose of our biomarker study.

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References

1. Akai M, Doi T, Fujino K, Iwaya T, Kurosawa H, Nasu T (2005) An outcome measure for Japanese people with knee osteoarthritis. J Rheumatol 32:1524–1532
2. Takahashi M, Kushida K, Hoshino H, Suzuki M, Sano M, Miyamoto S, Inoue T (1996) Concentrations of pyridinoline and deoxypyridinoline in joint tissues from patients with osteoarthritis or rheumatoid arthritis. Ann Rheum Dis 55:324–327
3. Vilím V, Olejárová M, Machácek S, Gatterová J, Kraus VB, Pavelka K (2002) Serum levels of cartilage oligometric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. Osteoarthr Cart 10:707–713
4. Bobacz K, Maier R, Fialka C, Ekhart H, Woloszczuk W, Geyer G, Erlacher L, Smolen J, Graninger WB (2003) Is pro-matrix metalloproteinase-3 a marker for posttraumatic cartilage degradation ? Osteoarthr Cart 11:665–672
5. Yoshihara Y, Obata K, Fujimoto N, Yamashita K, Hayakawa T, Shimmei M (1995) Increased levels of stromelysin-1 and tissue inhibitor of metalloproteinases-1 in sera from patients with rheumatoid arthritis. Arthritis Rheum 38:969–975
6. Dingle JT, Page Thomas DP, King B, Bard DR (1987) In vivo studies of articular tissue damage mediated by catabolin/interleukin 1. Ann Rheum Dis 46:527–533
7. Karan A, Karan MA, Vural P, Erten N, Taşçioğlu C, Aksoy C, Canbaz M, Oncel A (2003) Synovial fluid nitric oxide levels in patients with knee osteoarthritis. Clin Rheumatol 22:397–399
8. Garnero P, Landewé R, Boers M, Verhoeven A, Van Der Linden S, Christgau S, Van Der Heijde D, Boonen A, Geusens P (2002) 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 46:2847–2856
9. Landewé R, Geusens P, Boers M, van der Heijde D, Lems W, te Koppele J, van der Linden S, Garnero P (2004) 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 50:1390–1399
10. Garnero P, Conrozier T, Christgau S, Mathieu P, Delmas PD, Vignon E (2003) Urinary type II collagen C-telopeptide levels are increased in patients with rapidly destructive hip osteoarthritis. Ann Rheum Dis 62:939–943
11. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E (2001) 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 60:619–626
12. Jordan KM, Syddall HE, Garnero P, Gineyts E, Dennison EM, Sayer AA, Delmas PD, Cooper C, Arden NK (2006) Urinary CTX-II and glucosyl-galactosyl-pyridinoline are associated with the presence and severity of radiographic knee osteoarthritis in men. Ann Rheum Dis 65:871–877
13. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J, Rodan GA, Duong le T (2004) 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 50:1193–1206
14. Shiozaki H, Koga Y, Omori G, Yamamoto G, Takahashi HE (1999) Epidemiology of osteoarthritis of the knee in a rural Japanese population. Knee 6:183–188
15. Shiozaki H, Koga Y, Omori G, Tamaki M (1999) Obesity and osteoarthritis of the knee in women; results of Matsudai Knee Osteoarthritis Survey. Knee 6:189–192
16. Mouritzen U, Christgau S, Lehmann HJ, Tankó LB, Christiansen C (2003) 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 62:332–336
17. Lehmann HJ, Mouritzen U, Christgau S, Cloos PA, Christiansen C (2002) Effect of bisphosphonates on cartilage turnover assessed with a newly developed assay for collagen type II degradation products. Ann Rheum Dis 61:530–533
18. Sone T, Miyake M, Takeda N, Fukunaga M (1995) Urinary excretion of type I collagen crosslinked N-telopeptides in healthy Japanese adults: age- and sex-related changes and reference limits. Bone 17:335–339
19. Dequeker J, Boonen S, Aerssens J, Westhovens R (1996) Inverse relationship osteoarthritis–osteoporosis: What is the evidence? What are the consequences? Br J Rheumatol 35:813–818
20. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, Levy D, Felson DT (2000) Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. J Rheumatol 27:1032–1037
21. Bettica P, Cline G, Hart DJ, Meyer J, Spector TD (2002) Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. Arthritis Rheum 46:3178–3184