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).

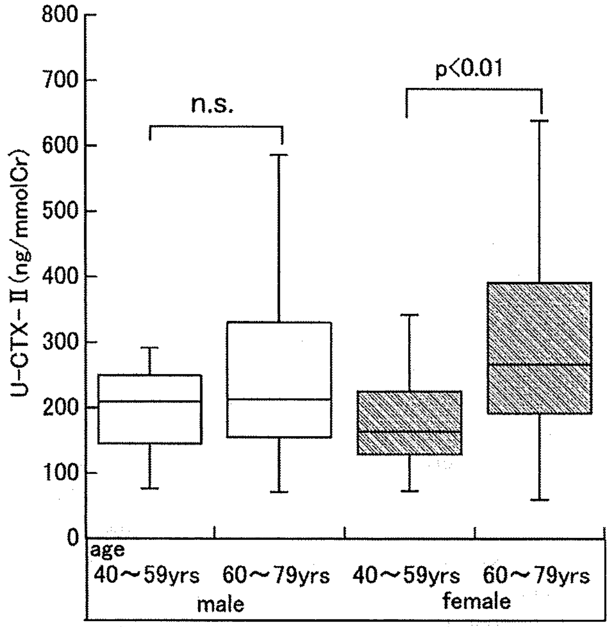

Fig. 1 Relationship between age (40–59:60–79 years) and the urinary CTX-II level in male and female subjects. Each *box* represents the 25th/50th (median) to 75th percentiles. The *lines outside the box* represent the 10th and 90th percentiles

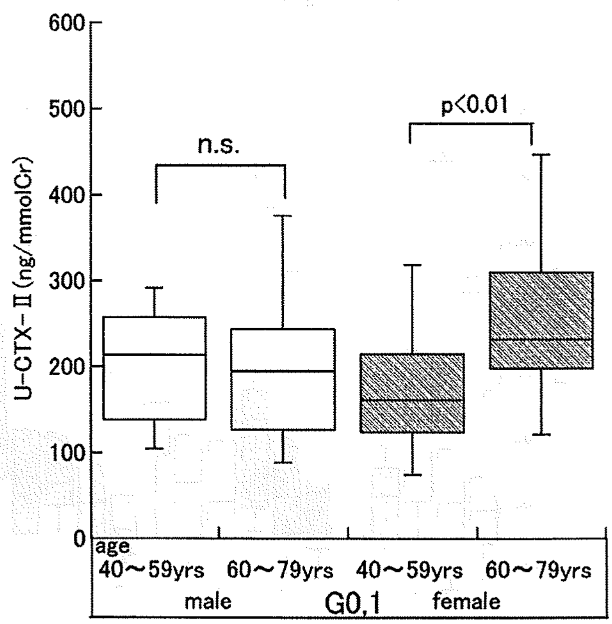

Fig. 2 Relationship between age (40–59:60–79 years) and the urinary CTX-II level in male and female subjects with knee X-ray OA Grade 0 and 1

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).

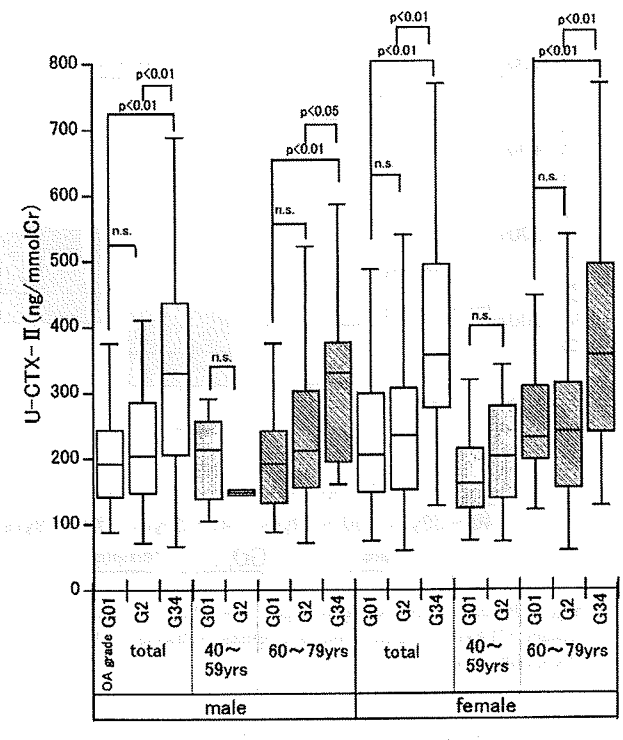

Fig. 3 Relationship between the knee X-ray OA grade and the urinary CTX-II level in male and female subjects. A statistical analysis was performed between different OA grade groups in each age group

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).

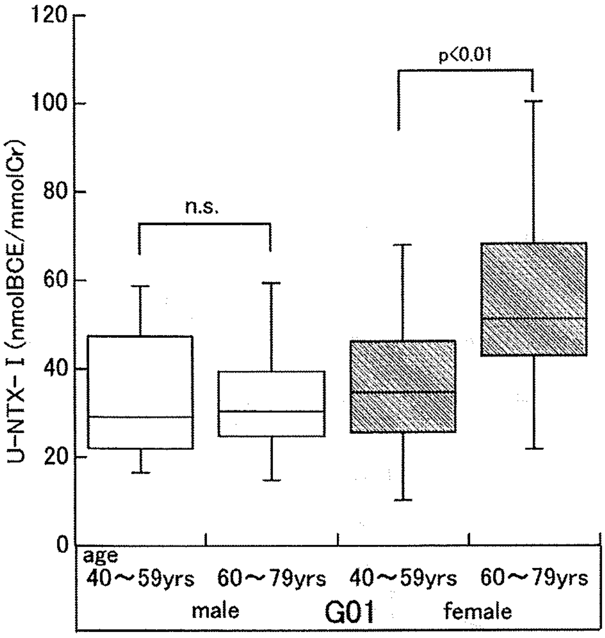

Fig. 4 Relationship between age (40–59:60–79 years) and the urinary NTX-I level in male and female subjects with knee X-ray OA Grade 0, 1

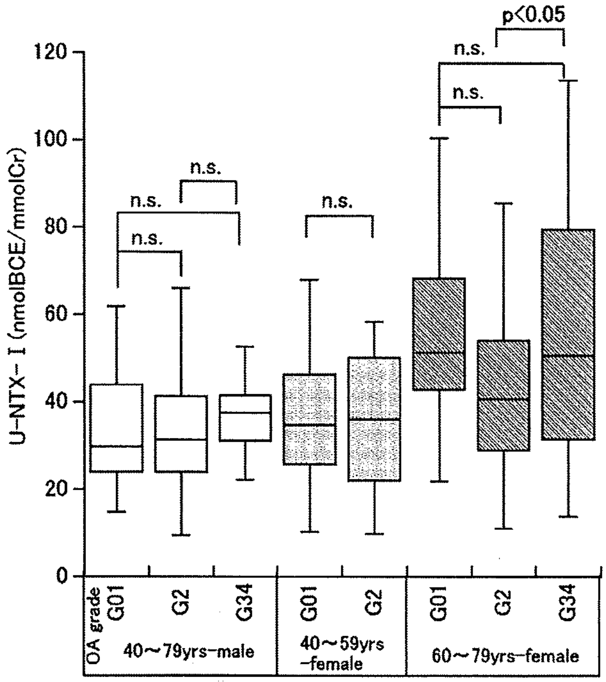

Fig. 5 Relationship between knee the X-ray OA grade and urinary the NTX-I level in male and female subjects

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

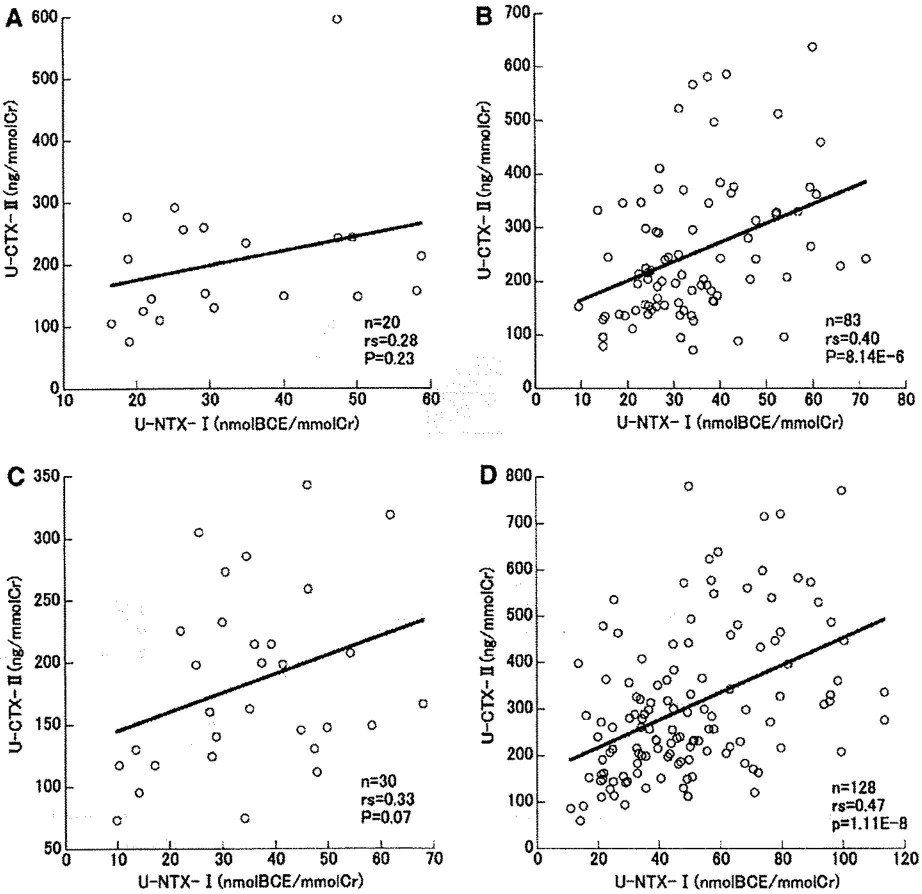

Fig. 6 Correlation between the urinary NTX-I level and the urinary CTX-II level in **a** male aged 40–59 years, **b** male aged 60–79 years, **c** female aged 40–59 years, and **d** female aged 60–79 years. Significant differences ($P < 0.05$) were observed only in 60–79 years of both genders

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.

Acknowledgments We express our gratitude to all the people involved with the Matsudai district resident health check and to all the residents who consented and provided samples. We also wish to thank SLR, Inc., for their cooperation in collecting the samples and performing the measurements and all the staff at Niigata Kobari Hospital for their cooperation in conducting knee examinations. This work was supported by Grant-in-Aid for Scientific Research B (19390389).

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

Journal of Biomechanics 42 (2009) 2818–2822

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Short communication

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

Koichi Kobayashi [a,*], Makoto Sakamoto [a], Yuji Tanabe [b], Akihiro Ariumi [c], Takashi Sato [c], Go Omori [d], Yoshio Koga [c]

[a] *Department of Health Sciences, Niigata University School of Medicine, 2-746 Asahimachi-dori, Chuo-ku, Niigata 951-8518, Japan*
[b] *Department of Mechanical Engineering, Niigata University, 2-8050 Ikarashi, Nishi-ku, Niigata 950-2181, Japan*
[c] *Department of Orthopaedic Surgery, Niigata Kobari Hospital, 3-27-11 Kobari, Nishi-ku, Niigata 950-2022, Japan*
[d] *Center for Transdisciplinary Research, Niigata University, 2-8050 Ikarashi, Nishi-ku, Niigata 950-2181, Japan*

ARTICLE INFO

Article history:
Accepted 11 August 2009

Keywords:
Joint
3D position measurement
Accuracy
Lower leg Alignment
Biplanar radiography

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

* Corresponding author. Tel./fax: +81 25 227 0935.
E-mail address: kobayasi@clg.niigata-u.ac.jp (K. Kobayashi).

0021-9290/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jbiomech.2009.08.022

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:

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

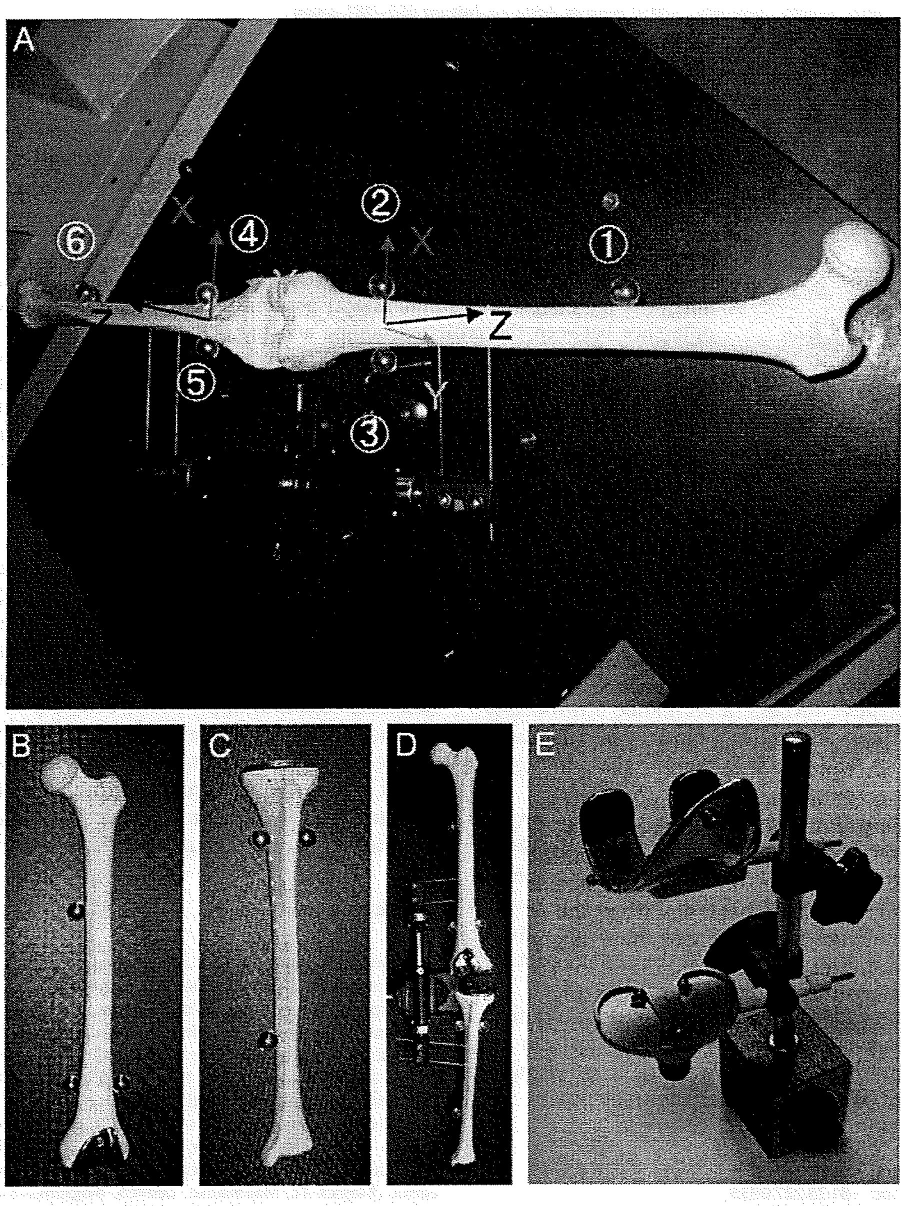

Fig. 1. Set-up for measurement of relative position. (A) The sawbone femur and tibia were immobilized using an external fixation device. (B) Femur with the femoral component attached. (C) Tibia with tibial component attached. (D) The implanted femur and tibia were immobilized using an external fixation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

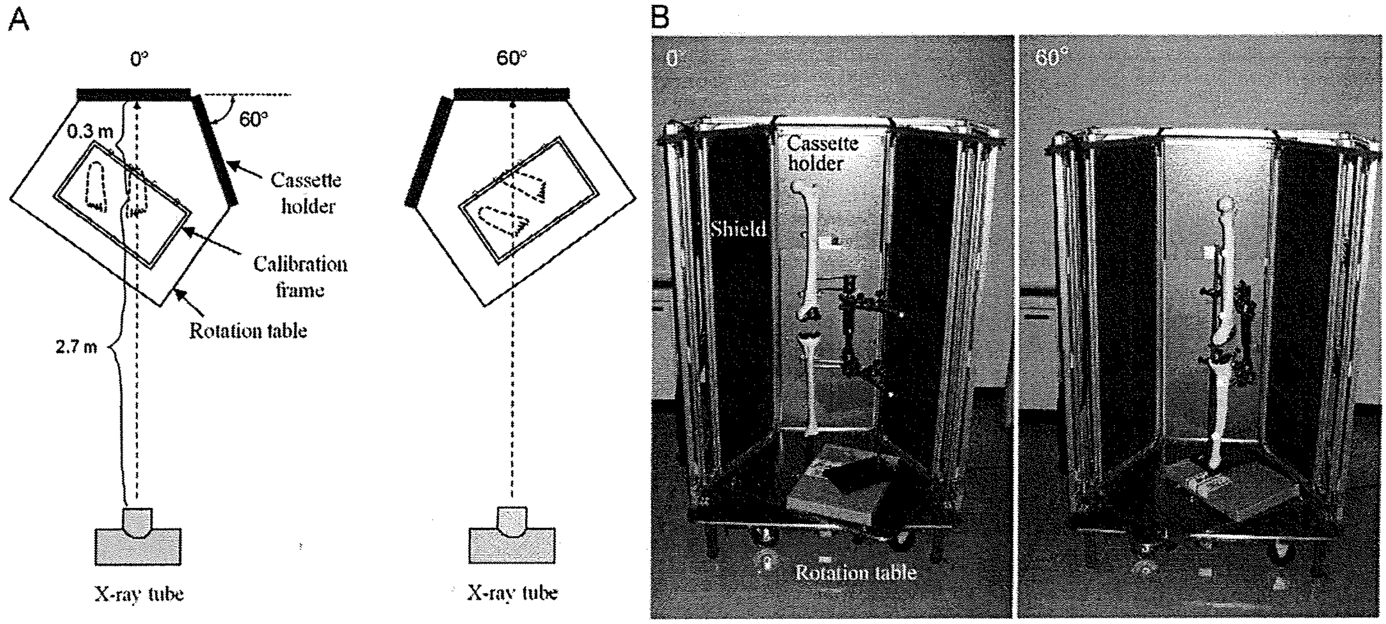

Fig. 2. Calibration set-up for the rotation table for bi-plane radiography (A). An acrylic frame with 72 spherical stainless markers attached was used for calibration. Half of the 72 markers were attached to the frontal surface, and the other half attached to the back surface to cover the volume of the 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).

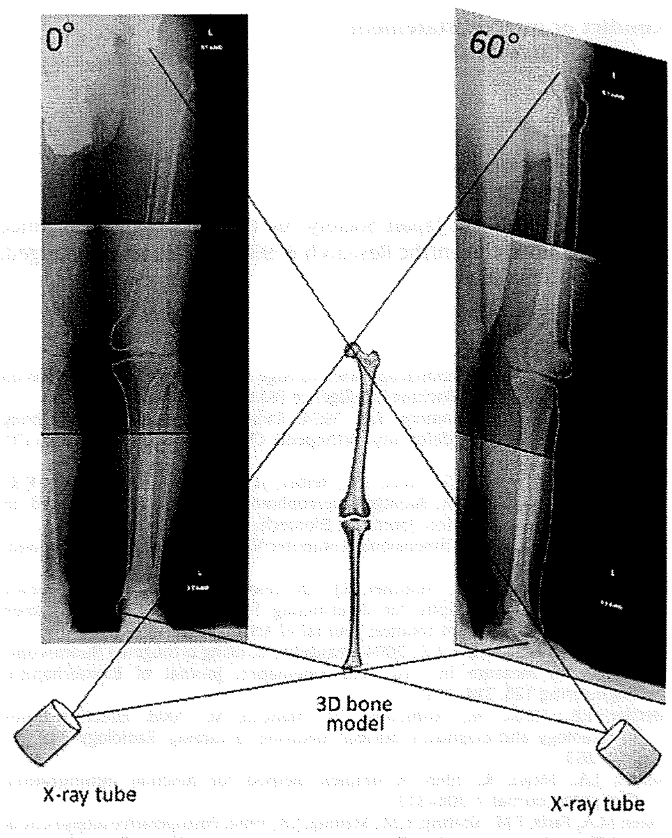

Fig. 3. Synthetic biplanar X-ray system. Projected outline points of each 3D model were the finite edge points of the 2D shadow created from the projections of all visible triangular surfaces of the 3D model.

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.

Acknowledgements

Funding from the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research B19360046) is acknowledged.

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.

■ 特集「新しい技術開発による運動機能向上への挑戦」

セッティング式筋力測定・訓練器による膝伸展筋力と筋力発揮パターンの解析

縄田　厚[1)]　稙丸　舞[1)]　岩嵜徹治[1)]　渡辺博史[2)]
古賀良生[3)]　大森　豪[4)]　遠藤和男[5)]

アルケア株式会社医工学研究所[1)]，新潟こばり病院リハビリテーション部[2)]，同整形外科[3)]，
新潟大学超域研究機構[4)]，新潟医療福祉大学健康科学部[5)]

要旨　大腿四頭筋訓練に有効な機器を開発し，それを用いて高齢者に対する膝伸展筋力の効果的なトレーニングメニューを決定するため，膝伸展筋力に加え膝伸展筋力発揮波形について解析した．その結果，加齢に伴う変化は筋力以外に膝伸展筋力発揮における立ち上がり時間においても加齢等に伴う低下を確認した．高齢者の膝伸展筋力トレーニングにおいて膝伸展筋力と立ち上がり時間との双方を考慮した設定が有用な方法と考える．

Abstract　We developed a new instrument for quadriceps power rehabilitation. With this instrument, we performed an epidemiological study measuring isometric knee extensor muscle strength in 1465 subjects (843 females and 622 males, aged 23 to 93 years) with or without knee osteoarthritis.

Maximum knee extensor muscle strength was higher in males than in females, and it decreased above the age of 50 in both sexes. Speed of extension (time duration of 20 to 80% to maximum knee extensor muscle strength) prolonged above the age of 60. Maximum knee extensor muscle strength was less in knee OA group and speed of extension also prolonged in OA group.

We think that the new instrument can provide some useful information on quadriceps power rehabilitation by measuring both knee extensor muscle strength and speed of extension.

Key words：変形性膝関節症（knee osteoarthritis），膝伸展筋力（knee extensor muscle strength），大腿四頭筋セッティング訓練（quadriceps setting exercise）

はじめに

高齢者の転倒や変形性膝関節症（以下，膝OA）は，膝伸展筋力の低下と関連性があるとされ[1,8,10)]，発症予防や症状改善のために膝伸展筋力訓練が推奨されている[6,11)]．一般的に膝伸展筋力訓練では，筋力の最大値を計測し，訓練時の負荷力の設定を行っていることが多いが，筋肉の反応や調整機能を考えた場合，筋力の最大値のみでは不十分であると考

Analysis of knee extensor muscle strength and its exertion pattern by a newly developed muscle strength measuring and training instrument
Atsushi NAWATA, Mai AKIMARU, Tetsuji IWASAKI, Hiroshi WATANABE, RPT, Yoshino KOGA, MD, Go OMORI, MD and Kazuo ENDO, MD
連絡先：〒131-0046 東京都墨田区京島 1-21-10　アルケア株式会社医工学研究所　縄田　厚　電話 03-3611-1101

えられる．われわれは，膝伸展筋力の評価と効果的な訓練のために筋力の最大値に加えて筋力発現の特性についての考慮が重要と考えた．本研究では，膝 OA の集団検診受診者を対象に最大膝伸展筋力の定量評価および筋力発揮波形を分析し，高齢者特有の因子が存在するか否かを検討した．

対象および方法

1．対象

対象は，新潟県十日町市松代地区で 2007 年に行われた住民膝検診受診者で同意の得られた 1,465 名で，性別の内訳は，女性 843 名，男性 622 名であった．対象者の年齢別構成は 23 ～ 93 歳である．男女ともに 70 歳代が最も多く，平均年齢は女性 68.2 ± 13.2 歳，男性 66.2 ± 13.0 歳であった．

分析に用いた対象は，膝伸展筋力測定を実施した 2883 膝であり，性別の内訳は，男性 1228 膝，女性 1655 膝，左右の内訳は，左 1441 膝，右 1442 膝である．

2．測定器の概略

測定に使用した簡易筋力測定訓練器（QTM-05F）（以下，測定器）は，簡便な方法で安全性に優れている大腿四頭筋セッティングの手法（枕つぶし運動）[13] を基本として開発した（図 1）．膝屈曲約 30 度に対応した膝窩部の枕部構造に，荷重計測にロードセルを用い，膝伸展筋力を経時的測定ができる．筋力値の測定データの精度は ± 0.1 kg，サンプリングスピードは 250 ms，計測可能限界は 135 kg である．

測定器の機能として負荷量（kg）・負荷時間（s）・回数（回）・セット数（set）を入力し，訓練中に目標の負荷量に達した場合，音楽と表示で使用者に訓練状態を理解や目標負荷量を一定量越えた場合にオーバーロードを警告音で知らせ無理のない訓練の管理を可能とした．訓練中の筋力データも自動保存され，機器とパソコンをつなげることで専用ソフトによりそのデータの処理を可能とした．

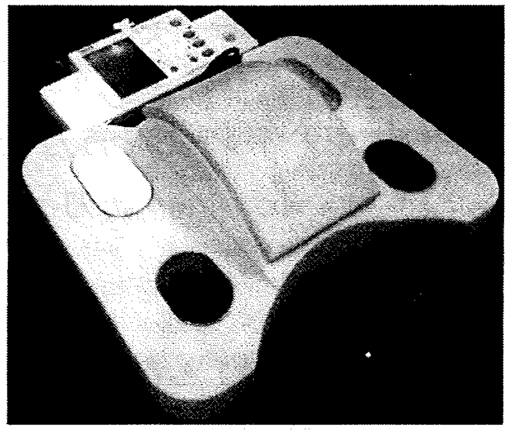

図 1　簡易筋力測定訓練器
機器は，本体計測部と表示・操作部にて構成され，表示・操作部の指示にて操作できる構造となっている．

3．方法

対象者全員に膝伸展筋力測定と立位膝関節前後 X 線撮影（以下 X 線撮影）を行った．筋力測定は，測定器を使用し，左右の膝を測定した．筋力測定の肢位は，膝屈曲約 30 度の長座位で膝窩部に測定器を配置し，骨盤帯と下腿遠位部を非伸縮性バンドで固定した．筋力の測定は，測定の前に理学療法士が各対象者に説明を実施し，この肢位で対象者が膝伸展運動を行った際，膝窩部で測定器を押し付ける力を左右 1 回ずつ 5 秒間計測し（図 2），5 秒間中の膝伸展筋力波形図として取得した．

取得した膝伸展筋力波形図より，最大膝伸展筋力と波形立ち上がり時の区間時間（以下，区間時間）を算出し，最大膝伸展筋力と区間時間を性別，年代別，膝 OA grade 別で比較した．膝 OA の病期分類は，X 線像から Kellgren の分類[3] を参考に 5 段階で同一の医師

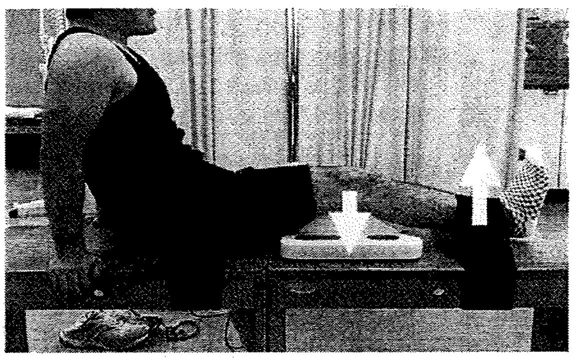

図 2　筋力測定（右膝）
骨盤と下腿遠位部を非伸縮バンドで固定して，膝伸展運動をさせた際の膝窩部に発生する力を測定した．

表 1　X 線像による膝 OA の病期分類

OA grade	裂隙狭小化	骨棘形成等
Grade 0	(－)	(－)
Grade Ⅰ	(－)	(＋)
Grade Ⅱ	＜1/2	(＋)
Grade Ⅲ	＞1/2	(＋)
Grade Ⅳ	閉鎖	(＋)

Kellgren に準じて 5 段階評価で同一の医師が判定した．

表 2　OA についての 2 群の内訳

	左膝		右膝	
	非 OA 群	OA 群	非 OA 群	OA 群
男性	446 膝	381 膝	466 膝	362 膝
女性	424 膝	190 膝	435 膝	179 膝
計	870 膝	571 膝	901 膝	541 膝

非 OA 群：grade 0，Ⅰ，OA 群：grade Ⅱ以上

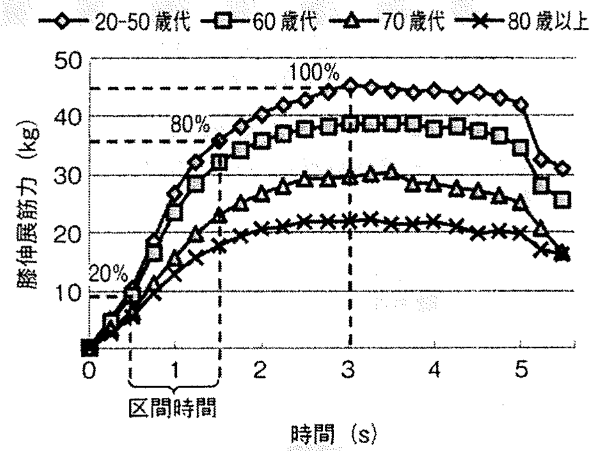

図 3　膝伸展筋力波形図（男性）

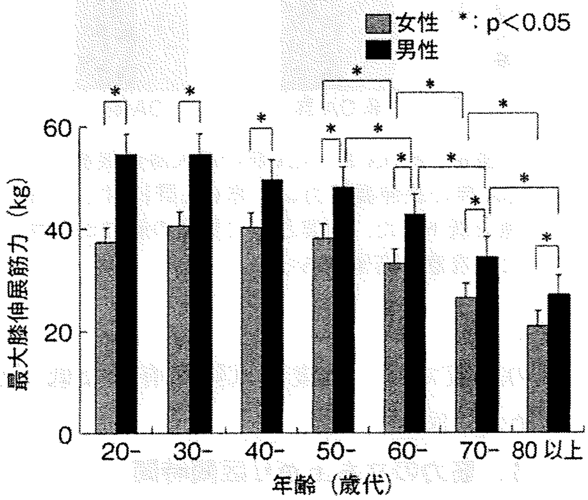

図 4　性別・年代別最大膝伸展筋力
男女ともに 50 歳代以降で有意な筋力低下を認めた．

が判定した（表 1）．また膝 OA grade が 0，Ⅰを非 OA 群，Ⅱ以上を OA 群の 2 群に分けて（表 2），最大膝伸展筋力と区間時間との関係について検討した．統計学手法は，一元配置分散分析と対応のない t 検定を使用し，有意水準は 5%未満とした．

結　果

1．膝伸展筋力波形

膝伸展筋力波形は，伸展筋力の最大値（ピーク）到達前までは傾きが大きく，ピーク後にプラトー状態になり，その後低下する形態を示した．男性の膝伸展筋力波形の結果を年代別平均値で見ると 20 ～ 50 歳代では，ほぼ同じ波形を示した．ただし，20 ～ 50 歳代の各群では，波形のばらつきが大きい結果であった．50 歳代以降は，加齢に伴い波形のピークが低下した（図 3）．この傾向は女性でも同じであった．

2．最大膝伸展筋力

膝伸展筋力波形において最大値を最大膝伸展筋力とした．性別の比較では，すべての年齢層にて女性が有意に低い値であった．年代

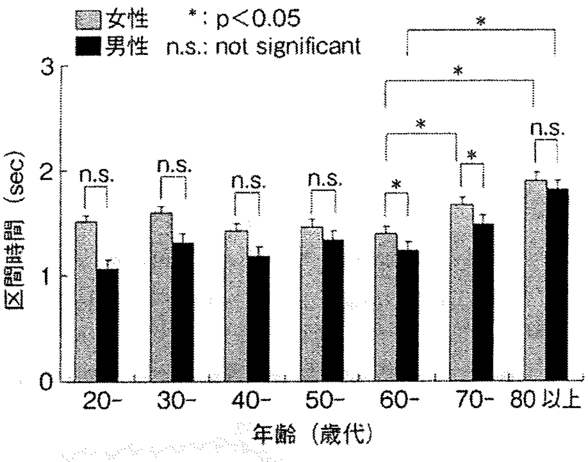

図 5　性別・年代別区間時間
男女ともに 60 歳代以降において区間時間が有意に延長した.

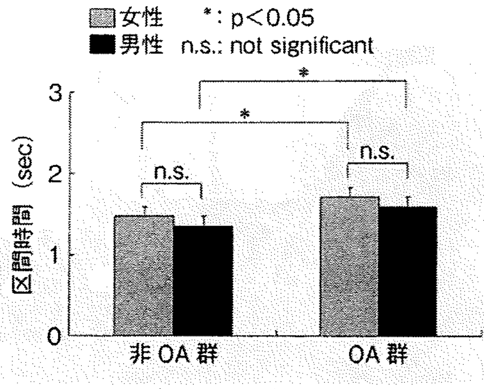

図 7　非 OA 群・OA 群の区間時間
OA 群の区間時間は，非 OA 群に対して有意に延長した．両群ともに区間時間には有意な性差を認めなかった.

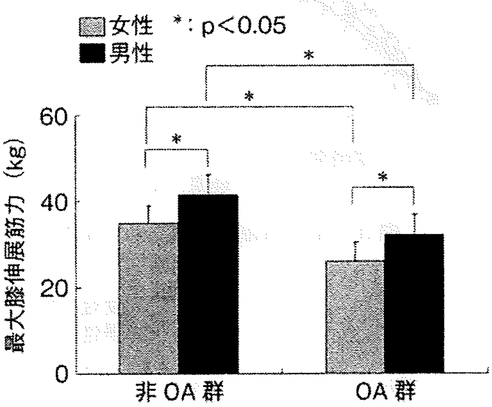

図 6　非 OA 群・OA 群の最大膝伸展筋力
OA 群の膝伸展筋力は，非 OA 群に対して有意な低下した．両群ともに男性の筋力が女性より有意に高値であった.

別の比較では，50 歳代以降に有意な低下を認めた（図 4）.

3．筋力の立ち上がり区間時間

膝伸展筋力波形の立ち上がりは，筋力発揮初期には被検者の理解度等に影響される可能性があること，最大値付近はプラトー区間で時間的変化が少なくなっていることから定義する区間について検討し，最大膝伸展筋力を 100％とした場合の 20 ～ 80％区間とすると最も良く立ち上がり時間を示したため，20 ～ 80％区間を「区間時間」として定義した（図 3）.

区間時間の性別の比較では，20 ～ 50 歳代において有意な性差はなく，60 歳以降において女性の区間時間が男性より有意に延長した．しかし 80 歳代については，性差はなかった．年代別の比較においても 20 ～ 50 歳代において有意な変化はなく，60 歳代以降で加齢に伴い延長した（図 5）.

4．膝 OA との関連

非 OA 群・OA 群の 2 群間における最大膝伸展筋力の比較で，OA 群は性別にかかわらず非 OA 群と比較して有意な低下が認められた（図 6）.

非 OA 群・OA 群の 2 群間における区間時間の比較にて，両群とも性差を認めず，男女とも OA 群の区間時間が非 OA 群に対して有意に延長を認めた（図 7）.

考　察

今回開発した測定器は，簡便な機構でありながら，Cybex のデータとも相関性の高い筋力の定量評価が可能であり[12]，大腿四頭筋の詳細な定量評価および膝 OA のリハビリテーションにおける筋力訓練においても有効性が

高いと考えられる[13].

今回の研究において最大膝伸展筋力は，測定した各年代において男性で有意に高く，さらに男女ともに50歳以降経年的に減少した．この結果は，50～60歳以降で筋力が低下するとしたLarssonら[7]やCalmelsら[2]の報告と一致している．さらに非OA群とOA群の比較においては，OA群で有意な筋力低下が見られ，これまでの報告と同様に膝OAと大腿四頭筋力の関連性が示唆された[4,12]．一方20～40歳代では，最大膝伸展筋力の低下が認められなかったが，これが生理的な変化によるものなのかあるいは他の要因が影響しているものかについては，本研究では40歳以下の対象者が少ないために明らかにならなかった．

また今回，筋の活動性の機能の指標として区間時間を評価した結果，20～40歳の年齢層において差が認められず，60歳から延長する傾向にあったことから，高齢者の筋力を評価する際に筋力と異なる指標となると考える．長澤ら[9]は，高齢者に対して神経機能に関する下肢の敏捷性には性差があるとし，久野ら[5]は，加齢に伴い運動ニューロンの削減による運動単位の減少の要因を指摘し，高齢者の筋力訓練においては神経系要因も関与していると述べている．これらのことから膝伸展筋力の低下には筋出力の低下・末梢神経系の機能低下・筋動員力の低下が関与し，さらに区間時間の延長には，末梢神経系の機能低下・筋動員力の低下に関与しているものと考える．

以上の結果より，中高年の筋機能を評価するためには，最大膝伸展筋力に加え，筋力の立ち上がり区間時間を含めた経時的な波形で筋力を分析することが有用と考えられる．

今後は，膝OAとの関連性を詳細に検討したうえで，それに対応した筋力訓練プログラムの作成を行いたいと考える．

まとめ

1．開発した簡易筋力測定訓練器を用いて膝伸展筋力測定を実施し，最大膝伸展筋力の定量評価および筋力発揮波形にて，加齢変化や膝OAとの関係を検討した．

2．膝伸展筋力波形は，男女とも50歳代以降加齢に伴うピークの低下を認めた．また，最大膝伸展筋力は男女とも50歳代以降および膝OA群で低下した．さらに，区間時間は，男女とも60歳代以降および膝OA群で延長を認めた．

3．区間時間の延長は，神経-筋活動の低下による可能性があり，中高年の筋機能を評価するためには，最大膝伸展筋力に加え，立ち上がり区間時間を含めた波形で筋力を分析することが有用であると考えられる．

文　献

1) Brown M. et al: The relationship of strength to function in the older adults. J Geribtol. **50A**: 55-59, 1995.
2) Calmels P. et al: Cross-sectional study of muscle strength and bone mineral density in a population of 106 women between the ages of 44 and 87 years: relationship with age and menopause. Eur J Appl Physiol. **70**: 180-186, 1955.
3) Kellgren JH. et al: Radiological assessment of osteoarthritis. Ann Rheum Dis. **16**: 494-501, 1957.
4) 古賀良生ほか：変形性膝関節症の悪化要因の疫学的検討．関節外科　**24**：51-55，2005.
5) 久野譜也ほか：高齢者の筋特性と筋力トレーニング．体力医学　**52**：17-30，2003.
6) 黒澤　尚ほか：変形性膝関節症に対する大腿四頭筋訓練：外来初診患者の2年以上，最長7年間の経過．臨床スポーツ医学　**22**：663-671，2005.
7) Larsson L.: Morphological and functional characteristics of the aging skeletal muscle in man. Acta Physiol Scand. suppl **457**: 1-36, 1978.

8) Lord SR. et al: Physiological factors associated with falls in older community-dwelling women. J Am Geriatr Soc. **42**: 1110-1117, 1994.
9) 長澤吉則ほか：中・高年者における筋力発揮調整能と体力との関係及びその性差．体力科学 **50**：425-436．2001．
10) Slemenda C. et al: Quadriceps weakness and osteoarthritis the knee. Ann Intern. **127**: 97-104, 1997.
11) 清水直史ほか：伸展下肢挙上訓練による変形性膝関節症の治療．整形外科 **42**：646-654．1991．
12) 渡辺博史ほか：膝伸展筋力の加齢変化と変形性膝関節症との関連．運動・物理療法 **18**：286-291．2007．
13) 渡辺博史：筋力強化の実際．古賀良生編．変形性膝関節症―病態と保存療法．南江堂．東京．pp 161-175．2008．

balt6/zsp-spine/zsp-spine/zsp00509/zsp7791-09z | xppws | S=1 | 1/12/09 | 10:42 | Art: BRS202478 | Input-SM
SPINE Volume 34, Number 5, pp 000–000

AQ: 1

Nocturnal Leg Cramps

A Common Complaint in Patients With Lumbar Spinal Canal Stenosis

Morio Matsumoto, MD,* Kota Watanabe, MD,† Takashi Tsuji, MD,† Ken Ishii, MD,†
Hironari Takaishi, MD,† Masaya Nakamura, MD,† Yoshiaki Toyama, MD,†
Kazuhiro Chiba, MD,† Takehiro Michikawa, MD,‡ and Yuji Nishiwaki, MD‡

Study Design. Questionnaire survey on leg cramps for patients with lumbar spinal canal stenosis (LCS).

Objective. To evaluate the prevalence of leg cramps in patients with LCS treated surgically and the relationship between leg cramps and the surgical outcomes.

Summary of Background Data. Although it has been anecdotally reported that LCS patients have suffered from leg cramps, the true prevalence remains unknown.

Methods. One hundred twenty LCS patients who underwent decompression surgery (men 85, women 35, mean age 73.5) and 370 elderly subjects from the general population (men 162, women 208, mean age 75.6) were enrolled in the study. The participants filled in a questionnaire regarding: (all participants) (1) experience of leg cramps, (2) frequency and time of the day of the cramp attacks; (for LCS patients only), (3) changes in cramps before and after surgery, (4) activities of daily living disturbance because of leg cramps, (5) satisfaction with surgery and walking ability, (6) the Roland-Morris Disability Questionnaire, and (7) the Oswestry Disability Index.

Results. Eighty-five (70.8%) patients with LCS and 137 (37.2%) of the control population experienced leg cramps (age and sex adjusted odds ratio; 4.6, $P < 0.01$). Leg cramps occurred once or twice a week in 34.9% of the LCS group and once in several months in 44.5% of the control group, and occurred nocturnally in 73.3% of the LCS patients and in 91.6% of the control group. In LCS patients, leg cramps improved after surgery in 18.2%, remained unchanged in 45.5%, and worsened in 26.1%, and activities of daily living were disturbed in 47.6%. There was no significant difference in satisfaction with surgery, the Oswestry Disability Index, the Roland-Morris Disability Questionnaire scores, or walking ability between the LCS patients with or without leg cramps.

Conclusion. LCS patients had significantly more frequent attacks of nocturnal leg cramps than the control population, and leg cramps disturbed the quality of the patients' life, and they rarely improved after decompression surgery. Leg cramps should be recognized as one of the symptoms of LCS, which disturb the patients' quality of life.

Key words: leg cramp, lumbar spinal canal stenosis, decompression surgery, nocturnal. **Spine 2009;34: 000–000**

From the Departments of *Advanced Therapy for Spine and Spinal Cord Disease, †Orthopaedic Surgery, and ‡Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan.
Acknowledgment date: July 3, 2008. Revision date: August 15, 2008. Acceptance date: August 18, 2008.
The manuscript submitted does not contain information about medical device(s)/drug(s).
Institutional funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.
Address correspondence and reprint requests to Morio Matsumoto, MD, Department of Advanced Therapy for Spine and Spinal Cord Disease, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan; E-mail: morio@sc.itc.keio.ac.jp

Neurogenic claudication, back and leg pain are the most common symptoms in patients with lumbar spinal canal stenosis (LCS), and they can be managed successfully by aggressive conservative treatments and/or surgery in the majority of patients. In addition to these frequently observed symptoms, patients with LCS sometimes complain of paresthesia, chillness, and restless leg sensation in their lower extremities, which have not, to date, attracted wide attention of spine care professionals. One of such complaints is leg cramps, which are acute involuntary painful contractions of the muscles in the lower extremities, and are likely to affect the elderly population as well as athletes and pregnant women.[1–6] Several general population surveys have reported that leg cramps occur in 38% to 50% of the elderly population.[1–4] Although their etiology remains to be clarified, leg cramps have been reported to be associated with neuromuscular diseases, diabetes, hyperthyroidism, hypertension, hypocalcaemia, hypokalaemia, vascular diseases, and some medications including diuretics, statins, steroids, and nifedipine, β-blockers, and so on.[2,6,7] To date, there have been few reports regarding the relationship between leg cramps and LCS, and it remains unknown whether surgical interventions have any impact on leg cramps in patients with LCS.

The purpose of this study was to elucidate the prevalence of leg cramps in patients with LCS and the relationships between leg cramps and the outcome of surgery in such patients. Our hypotheses are that the prevalence of leg cramps is higher in patients with LCS than the general population, and that surgery improves leg cramps.

■ Materials and Methods

During the period from 2000 to 2006, 271 patients with LCS underwent 1- or 2-level posterior decompression surgery without fusion. Of these patients, those who satisfied the following criteria were included in this study: (1) Patients with typical signs and symptoms of LCS (leg pain, neurogenic claudication) that was confirmed on magnetic resonance imaging and myelography; (2) those without any history of previous lumbar spine surgeries; (3) those without severe scoliosis (Cobb angle >20°) or spondylolisthesis (% slip >20%) which required instrumented fusion; and (4) those without any history of neuromuscular diseases such as cerebral palsy, congenital, and acquired myopathy, *et cetera*. These criteria were satisfied by 201 patients, to whom the questionnaire was mailed, inviting them to participate in this study.

Three hundred seventy elderly subjects from the general population without any history of back surgery, who had undergone a general health checkup and completed the question-

<zjs;Epidemiology> • <zjss;Epidemiology> • <zdoi;10.1097/BRS.0b013e31818f953c>
Lumbar spinal canal stenosis patients had significantly more frequent attack of nocturnal leg cramps than the control town populations. Leg cramps made the patients' life disturbed, and it did not

naire served as the controls. All participants in both groups filled in the questionnaire regarding: (1) Experience of leg cramps; (2) frequency and time of the day of cramp attack; (3) area of cramps; and (4) walking ability. Only the LCS patients filled in the questionnaire regarding: (5) changes in cramps before and after surgery; (6) residual sciatica (evaluated by visual analogue scale, VAS 0–100 points) and numbness in the legs and feet; (7) activities of daily living (ADL) disturbance by leg cramps; (8) satisfaction with surgery; (9) the Roland-Morris Disability Questionnaire (RDQ)[8]; (10) the Oswestry Disability Index (ODI)[9];and (11) treatment for leg cramps (Table 1). A part of the questionnaire was originally developed for this survey by a group of orthopedic surgeons and public health scientists. Association of diabetes mellitus and hypertension, which are the most common comorbidities of elderly people and which have been reported to be associated with leg cramps[6,7,10] were also investigated. For the LCS patients, charts were also reviewed regarding surgical methods, medications, and perioperative complications.

Statistical Analyses

Stata9 software (Stata Corp., College Station, TX) was used for statistical analyses. The χ^2 test and a logistic regression analysis were used as the statistical tests to compare the difference in the prevalence of leg cramps between the LCS patients and the control population. A P value less than 0.05 was considered statistically significant.

■ Results

Comparison Between the LCS and Control Group

One hundred twenty LCS patients who responded to the mail were finally included to the present study. There were 85 men and 35 women with a mean age of 73.5 ± 8.0 years. The mean follow-up period after surgery was 3.6 ± 1.9 years (Table 2). In the control group, there were 162 men and 208 women with a mean age of 75.6 ± 6.5 years. There was a statistically significant difference in the male to female ratio, between the LCS patient group and the control group ($P < 0.001$). Eighty-five (70.8%) patients with LCS and 137 (37.2%) of the controls experienced leg cramps (age and sex adjusted odds ratio; 4.6, 95% confidence interval; 2.87–7.35, $P <$ 0.001) (Table 3). Regarding comorbidities, hypertension was observed in 35.8% of the LCS patients and 41% of the control subjects ($P = 0.39$), and diabetes in 14.2% and 6.2%, respectively ($P = 0.014$). When the odds ratio for leg cramps was determined after the adjustment by these comorbidities, its prevalence was still significantly higher in LCS patients than in the control subjects (4.87, 95% confidence interval, 3.01–7.88, $P < 0.001$).

Leg cramps occurred once or twice a week in 34.9% of the LCS group and once in several months in 44.5% of the control group, so that the frequency of leg cramps was significantly higher in the LCS group ($P < 0.001$). Leg cramps occurred at night during sleep in 73.3% of the LCS patients and 91.6% of the control group, and at night before sleep in 14.0% and 2.5%, respectively. Although leg cramps mostly occurred nocturnally in both groups, LCS patients had leg cramps while awake more frequently than control subjects. Leg cramps occurred mostly in the calves both in the LCS patients (74.4%) and in the control subjects (64.2%). The laterality of leg cramps was elicited only for the LCS patients. Thirty-five patients (40.7%) had leg cramps bilaterally, 28 (32.6%) in the left, and 18 (20.9%) in the right. With regard to walking ability, 58.3% of the LCS patients and 81.9% of control subjects could walk more than 1 km ($P < 0.001$).

Table 1. Questionnaire for LCS Patients and Control Subjects

Q1 Have you recently experienced cramps in the legs?
- Yes
- No

Q2 How often do you have leg cramps?
- More than once a d
- Once a d
- Once a several d
- Once a several wk
- Once a several mo
- Once a yr

Q3 What time of the day do you have leg cramps?
- During sleep (midnight to dawn)
- In the morning
- In the afternoon
- In the evening

Q4 Where do you have leg cramps most?
- Calf
- Shin
- Anterior thigh
- Posterior thigh
- Foot

Q5 How long can you walk?
- No limitation
- Longer than 1 km
- 500 m-1 km
- 100–500 m
- Less than 100 m

For LCS patients only

Q6 Do you have residual sciatic leg pain now?
- Yes (If yes, mark on visual analogue scale)
- No

Q7 Do you have numbness in the legs and feet?
- Yes
- No

Q8 Did you have changes in leg cramps after surgery?
- Better than before surgery
- Unchanged
- Worse than before surgery
- No cramps before or after surgery

Q9 Are you satisfied with surgery?
- Very satisfied
- Satisfied
- Intermediate
- Dissatisfied
- Very dissatisfied

For LCS patients with leg cramps only

Q10 On which side do you have leg cramps?
- Right
- Left
- Both

Q11 Do leg cramps disturb your activity of daily livings?
- Extremely disturbed
- Moderately disturbed
- Slightly disturbed
- Not so disturbed
- Never disturbed

Q12 What kind of treatment have you had for leg cramps
- Medications()
- Massage
- Acupuncture
- Physical therapy
- None