KL ≥ 2 and KL ≥ 3 knee OA separately with the presence of knee pain according to gender and age stratum.

Subjects and methods

SUBJECTS

The ROAD study is a nationwide OA prospective study constituted of population-based cohorts established in several communities in Japan. To date, we have completed creation of a baseline database including clinical and genetic information of 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 23–95 years (mean 70.6 years), who were recruited from listings of resident registration in three communities. Itabashi-ku, an urban community located in the east of Tokyo, had a population of 529,400/32 km^2 with 0.1, 25, and 75% of jobs in the primary industry (agriculture, forestry, fishing and mining), the secondary industry (manufacturing and construction), and the tertiary industry (service industry), respectively, and residents ≥65 years constituted 19.1% of the population. Hidakagawa-cho, a rural mountainous community located in the center of Wakayama, had a population of 11,300/330 km^2 with 29, 24 and 47% of jobs in the three industries above, and 30.5% were ≥65 years. Taiji-cho, a rural seacoast community located south of Wakayama, had a population of 3,500/6 km^2 with 13, 18, and 69% of jobs in the three industries, and those ≥65 years accounted for 34.9% of the total. Participants in the urban region were recruited from a cohort study[24] in which the participants were randomly drawn from the Itabashi-ward residents register database and the response rate in the age groups of 60 years or older was 75.6%. Participants in the mountainous and seacoast regions were recruited from listings of resident registration and the response rates in the age groups of 60 years or older were 68.4% and 29.3%, respectively. All participants provided written informed consent, and the study was conducted with the approval of ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as occupational career, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, arm length, bilateral grip strength and body mass index (BMI; weight [kg]/height^2 [m^2]). Medical information was taken by well-experienced orthopaedic surgeons (S.M. and H.O.) on systemic, local and mental status including information of knee, hip and low back pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. Knee pain was defined as that in and around the knee joint on most days during the past month. A self-recorded nutritional survey was also performed. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of knee, hip and lumbar spine were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). Mean height was 162.5 and 149.7 cm in men and women, respectively, in the ROAD study vs 162.6 and 149.9 cm in the Japanese general population. Weight was 61.3 and 51.8 kg vs 61.6 and 53.8 kg. Percentage of the population with a smoking habit was 26.4 and 3.2% vs 29.4 and 4.0%. From the baseline data of the overall participants, the present study analyzed 2,282 (817 men and 1,465 women) aged 60 years or older, after excluding six subjects with total knee arthroplasty.

RADIOGRAPHIC ASSESSMENT

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anterior–posterior X-ray beam was used to visualize the joint space properly. Knee radiographs were read without knowledge of participant clinical status by a single well-experienced orthopaedist (S.M.), and KL grade was defined using the KL radiographic atlas for overall knee radiographic grades[15]. The higher KL grade in both knees was designated as that of a participant. The radiographic knee OA with pain was defined as: (1) a subject reporting knee pain lasting at least 1 month with pain having last occurred within the current or previous year; and (2) radiographic OA in that painful knee. To evaluate the intraobserver variability of the KL grading, 100 randomly selected radiographs of the knee were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopeadic surgeons (S.M. & H.O.) using the same atlas for interobserver variability. The intra- and inter variabilities evaluated for KL grade (0–4) were confirmed by the kappa analysis to be sufficient for assessment (0.86 and 0.80, respectively). Further, to determine the prevalence of medial and lateral knee OA, knee radiographs were also read for JSN in the medial and lateral compartment separately according to the Osteoarthritis Research Society International (OARSI) atlas by a single well-experienced orthopaedist (S.M.)[25]. Medial OA was defined as present when a knee had a KL grade ≥2 and medial JSN score of ≥1 on a 0–3 scale. Lateral OA was defined as being present when a knee had a KL grade ≥2 and lateral JSN score of ≥1 on a 0–3 scale.

STATISTICAL ANALYSIS

The differences of age and BMI between men and women were examined by non-paired *t*-test. Differences in age, height, weight and BMI among the urban, mountainous and seacoast communities were determined using one-way analysis of covariance and Scheffe's test. To compare the prevalence of radiographic knee OA between men and women, we performed logistic-regression analysis after adjustment for age and BMI. Association of prevalence with age was determined by logistic-regression analysis after adjustment for BMI. Association of the variables such as age, BMI, gender and community with radiographic knee OA was evaluated by multivariate logistic-regression analysis. Logistic-regression analyses were used to estimate odds ratio and the associated 95% confidence interval (CI) of KL = 2 and KL ≥ 3 knee OA for pain compared with KL = 0 or 1 after adjustment for age, BMI, and community. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2,282 participants aged 60 years and older in the three cohorts of the ROAD study are shown in Table I. Men were significantly older than women in the overall population and in some communities. Although the seacoast residents tended to show higher body height and weight than the other two communities, BMI was comparable among the three communities and between genders.

Table II shows the prevalence of radiographic knee OA, knee pain and radiographic knee OA with pain in the overall population and subgroups classified by gender and community. In the overall population, prevalence of KL ≥ 2 and KL ≥ 3 OA was 61.9 and 20.6%, respectively, and that of knee pain was 32.8%. That of KL ≥ 2 and KL ≥ 3 OA with knee pain was 26.1% and 13.2%, respectively. The prevalence of unilateral and bilateral KL ≥ 2 knee OA was 12.3% and 49.5%, respectively, while the prevalence of unilateral and bilateral KL ≥ 2 knee OA with pain was 2.9% and 20.4%, respectively. We next analyzed the prevalence of

Table I
Characteristics of participants

	Men				Women			
	Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Number of subjects	817	396	266	155	1,465	740	433	292
Age, years	74.7 ± 6.1	77.3 ± 4.1	72.1 ± 6.2†	72.7 ± 7.4†	74.0 ± 6.4*	76.4 ± 4.8*	72.0 ± 7.0†	70.9 ± 6.8*†
Height, cm	161.3 ± 6.3	161.3 ± 5.9	160.3 ± 6.6	163.0 ± 6.1†	148.6 ± 6.2	148.6 ± 5.7	146.8 ± 6.4†	151.1 ± 5.9†
Weight, kg	60.1 ± 9.9	59.8 ± 8.3	59.3 ± 11.4	62.2 ± 10.6†	50.9 ± 8.9	50.7 ± 8.4	49.8 ± 9.7	53.0 ± 8.6†
BMI, kg/m^2	23.0 ± 3.3	23.0 ± 2.7	23.0 ± 3.8	23.3 ± 3.3	23.0 ± 3.7	22.9 ± 3.5	23.0 ± 4.1	23.2 ± 3.5

Data are means ± SD.
*$P < 0.05$ vs men in the corresponding group by non-paired *t*-test.
†$P < 0.05$ vs urban residents in the corresponding group by Scheffe's test.

Table II
Number (percentage) of participants with radiographic knee OA, knee pain, and their combination

	Overall	Men				Women			
		Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Radiographic knee OA									
KL ≥ 2	1,413 (61.9)	384 (47.0)	171 (43.2)	154 (57.9)	59 (38.1)	1,029 (70.2)*	521 (70.4)*	340 (78.5)*	168 (57.5)*
KL ≥ 3	470 (20.6)	110 (13.5)	27 (6.8)	45 (16.9)	38 (24.5)	360 (24.6)*	133 (18.0)*	139 (32.1)*	88 (30.1)*
Knee pain	748 (32.8)	197 (24.1)	100 (25.3)	76 (28.6)	21 (13.5)	551 (37.6)*	299 (40.4)*	176 (40.6)*	76 (26.0)*
Radiographic knee OA with pain									
KL ≥ 2	595 (26.1)	129 (15.8)	54 (13.6)	60 (22.6)	15 (9.7)	466 (31.8)*	237 (32.0)*	165 (38.1)*	64 (21.9)*
KL ≥ 3	301 (13.2)	63 (7.7)	21 (5.3)	29 (10.9)	13 (8.4)	238 (16.2)*	97 (13.1)*	93 (21.5)*	48 (16.4)*

*$P < 0.01$ vs men in the corresponding group by logistic-regression analysis after adjustment for age and BMI.

medial and lateral knee OA in the participants and found that they were 20.4 and 2.1% in men and 40.0 and 3.1% in women, respectively. Logistic-regression analysis after adjustment for age and BMI revealed that the prevalence of radiographic knee OA, knee pain, and their combination was significantly higher in women than in men. When the association of the prevalence with the age group (<65, 65–69, 70–74, 75–79 and ≥80) was examined, radiographic knee OA (KL ≥ 2 and KL ≥ 3) tended to increase with age in both genders [Fig. 1(A)]. Interestingly, the prevalence of knee pain was age-dependent in women, but not in men. Hence, that of radiographic OA with pain tended to be higher with age in women, but was affected little by age in men [Fig. 1(B)].

To examine the association of age, BMI, gender, and community with radiographic knee OA, knee pain, and their combination, we further performed logistic-regression analyses to estimate odds ratios and 95% CI (Table III). Age, BMI, and female sex were shown to be risk factors for all of them. Among the communities, mountainous area residents had a higher risk of KL ≥ 2 and KL ≥ 3 knee OA than urban residents, and seacoast area residents had a higher risk for KL ≥ 3 knee OA than urban residents.

We then evaluated the association between radiographic knee OA and knee pain in the designated knee. Figure 2 shows the percentage of subjects with knee pain in subgroups classified by radiographic OA severity: KL = 0/1, KL = 2, and KL ≥ 3. Although the percentage with pain was positively correlated with the radiographic severity, the difference between KL = 2 and KL ≥ 3 appeared to be greater than that between KL = 0/1 and KL = 2 in the overall population and all communities. When odds ratios of KL = 2 and KL ≥ 3 OA as compared to KL = 0/1 for the pain were estimated by logistic-regression analysis after adjustment for age, BMI, and community, KL = 2 OA was moderately but significantly associated with knee pain in both genders of the overall population (Table IV). However, KL ≥ 3 OA was much more strongly associated with knee pain not only in both genders of the overall population, but also in those of all age strata. Interestingly, although association of KL = 2 OA with pain was comparable between men and women, that of KL ≥ 3 OA with pain was stronger in

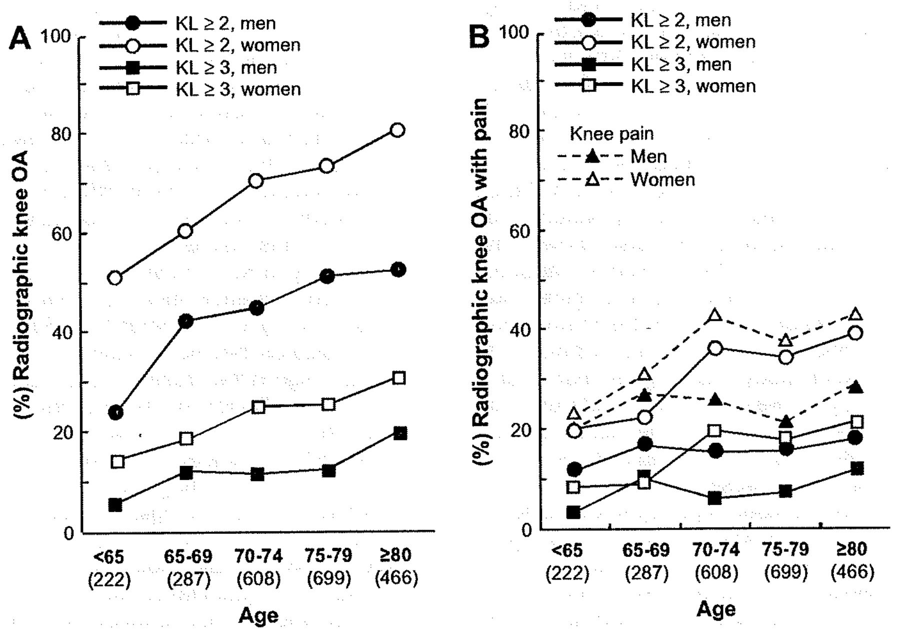

Fig. 1. (A) Percentage of subjects with radiographic knee OA (KL ≥ 2 or KL ≥ 3) in each age stratum (<65, 65–69, 70–74, 75–59 and ≥80). (B) Percentage of subjects with knee pain and radiographic knee OA (KL ≥ 2 or KL ≥ 3) with pain in each age stratum. The number of subjects in each age stratum is shown in parentheses.

Table III
Association of age, BMI, gender, and community with radiographic knee OA, knee pain and their combination

	Radiographic knee OA				Knee pain		Radiographic knee OA with pain			
	KL ≥ 2		KL ≥ 3				KL ≥ 2		KL ≥ 3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.09	1.07–1.11*	1.11	1.09–1.13*	1.04	1.02–1.06*	1.07	1.05–1.08*	1.09	1.07–1.12*
BMI, kg/m^2	1.14	1.11–1.18*	1.23	1.19–1.28*	1.18	1.14–1.21*	1.21	1.17–1.25*	1.24	1.20–1.29*
Women (vs Men)	3.28	2.71–3.97*	1.58	1.39–1.79*	2.05	1.68–2.51*	2.83	2.26–3.57*	2.59	1.92–3.53*
Community (vs Urban)										
Mountainous	2.64	2.08–3.35*	3.83	2.92–5.03*	1.27	1.02–1.58*	1.95	1.54–2.47*	2.84	2.09–3.85*
Seacoast	0.95	0.74–1.23	4.13	3.05–5.59*	0.56	0.42–0.73*	0.75	0.55–1.01	1.95	1.35–2.78*

The odds ratios were calculated by logistic-regression analysis after adjustment for all other variables.
*$P < 0.01$ OR = odds ratio, CI = confidential interval.

men. Considering that knee pain is more prevalent in women than in men (Tables II and III), we examined the association of gender with knee pain according to the KL grade. The odds ratio for knee pain of women compared with men estimated by a logistic-regression analysis after adjustment for age and BMI in the subgroup without radiographic knee OA (KL = 0/1) was comparable to or greater than that in those with radiographic knee OA (KL = 2 or KL ≥ 3) (Supplementary Table SI), suggesting independent backgrounds of knee pain between genders.

Discussion

The present study initially estimated the prevalence of knee OA in the Japanese elderly (≥60 years) using the baseline data of population-based cohorts in the ROAD study. The prevalence of KL ≥ 2 OA, the conventional diagnostic criterion of radiographic OA determined by the anterior–posterior view with standing position, was 47.0% and 70.2% in men and women, respectively (Table II), which was much higher than that of previous epidemiologic studies in elderly Caucasians in the USA and Europe[4–9], although not greatly different from African Americans and Chinese[10–12] (Supplementary Table SII). Caucasians seem to show a lower prevalence of radiographic OA than other races. In fact, the Johnston County study and the NHANES studies showed that African Americans had a higher prevalence of radiographic knee OA than Caucasians[6,8–10]. A previous Japanese community-based study, although with a rather small sample size, also showed that the prevalence of KL ≥ 2 knee OA of elderly Japanese women living in a seacoast area, Hizen-Oshima, was higher than that of Caucasian women in the Framingham study[13] (OR = 1.96, 95% CI = 1.50–2.56). Although the prevalence in the present study was higher than that in the Hizen-Oshima study, it was not much different from that of KL ≥ 2 knee OA of women in the seacoast area of the present study (46.4 vs 57.5%, Table II). Knee OA is a major public health issue causing impairment of activities of daily living and the number of patients with knee OA is suggested to be increasing with the advancing age of the population in Japan. According to the National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, this disease is now ranked second among the diseases that cause disabilities requiring support with activities of daily living.

In the present study, the prevalence of unilateral and bilateral KL ≥ 2 knee OA was 12.3% and 49.5%, respectively, while it was 12.5 and 34.1% in the Beijing study and 15.2 and 19.7% in the Framingham study, respectively[11]. The high prevalence of bilateral OA in this study was comparable to that in the Beijing study, but higher than that in the Framingham study. The high prevalence of bilateral knee OA may indicate that environmental or ethnic factors have an important role in knee OA in Japan and China. Zhang *et al.* described that the higher prevalence of bilateral knee OA in China could be due to the much more physically active lifestyle of the Chinese compared with US whites, especially among those who are elderly[11]. The higher prevalence of bilateral knee OA in Japan could also be due to lifestyle factors, because the Japanese traditional lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories; these positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA[26,27]. On the other hand, the prevalence of medial and lateral knee OA in the present study was 20.4 and 2.1% in men and 34.0 and 3.1% in women, respectively. The ratio of lateral to medial knee OA was 0.10 and 0.09 in men and women, respectively, while it was 0.13 and 0.20 in the Framingham study and 0.80 and 0.64 in the Beijing study, respectively[28]. In the present study, the prevalence of lateral knee OA was much lower than that of medial knee OA, which was comparable to that in the Framingham study, but lower than that in the Beijing study. There may be different etiologies of medial and lateral compartment OA in different ethnic populations. Further study is required to elucidate the underlying background of this disease.

Contrary to KL ≥ 2 OA, the prevalence of KL ≥ 3 OA was not much different in men from that in Caucasians, although it was still higher in women[4,5,7] (Supplementary Table SII). This indicates that the prevalence of KL = 2 knee OA is particularly high in the present study, especially in men. Considering the definition of the KL grade, this may mean that osteophytosis is more prevalent in elderly Japanese men, while JSN is comparable between the two ethnic groups. There is accumulating evidence that osteophytosis and JSN have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis was unrelated not only to JSN on plain radiographs, but also to cartilage loss measured by quantitative MRI[17]. Furthermore, our study on an experimental mouse model for OA has identified a cartilage specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during the OA progression[18,19]. Hence, there may be some risk factors that are specific to osteophytosis in elderly Japanese men.

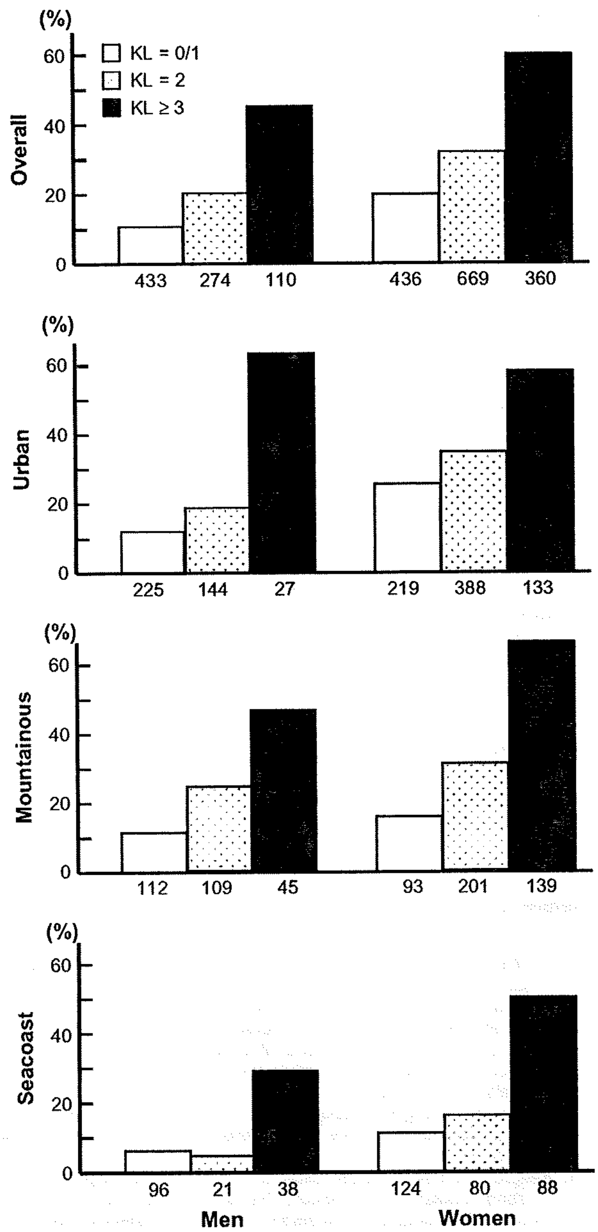

Fig. 2. Percentage of subjects with knee pain in each subgroup classified by the KL grade in the overall population and communities. The number of subjects in each subgroup is shown under the bars.

This study, the first analysis of the baseline data of the ROAD study, found that age and BMI were risk factors of radiographic knee OA (Table III), consistent with previous epidemiologic studies[1,29,30]. These factors may be related to the accumulation of mechanical stress on the knee joint. Female sex was also shown to be a strong risk factor, as in previous studies[4–8], possibly implicating an involvement of muscle strength to compensate the mechanical stress, as women are known to have less muscle strength than men in all decades[31]. Rural residency was also a risk factor of radiographic knee OA even after adjustment for age and BMI, indicating the involvement of other environmental factors like nutrition or occupation as well as genetic factors. In fact, the principle industries in the rural communities were

Table IV
Association of KL grade with knee pain according to age

	Overall		<65		65–69		70–74		75–79		≥80	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men												
KL = 2	1.96	1.27–3.05†	4.16	0.61–31.78	1.31	0.37–4.49	2.51	1.12–5.74	2.87	1.29–6.82*	0.58	0.24–2.11
KL ≥ 3	8.55	5.00–14.84†	9.39	0.52–231.69	7.91	1.72–41.02†	5.44	1.77–17.02	13.49	4.91–39.86†	8.24	2.77–27.02†
Women												
KL = 2	1.55	1.15–2.09†	1.45	0.53–4.04	1.36	0.62–3.06	1.59	0.92–2.79	1.45	0.84–2.58	1.87	0.92–4.04
KL ≥ 3	4.37	3.09–6.21†	4.13	1.17–14.80*	3.16	1.18–8.73*	5.60	2.93–10.97†	2.82	1.49–5.43†	7.36	3.25–17.66†

The odds ratio was calculated by logistic-regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age, BMI and communities.
$^*P < 0.05$; $^\dagger P < 0.01$.

farming, forestry and fishing, each of which demands physical activity and repetitive laborious use of the knee joints. Because the database of the ROAD study includes such detailed information of environmental factors including occupational career, lifestyle, and physical activity, as well as genetic information, further analyses will allow us to elucidate the risk factors and backgrounds of knee OA in more detail.

The present study also showed that the odds ratio for knee pain of $KL \geq 3$ OA was much higher than that of $KL = 2$ OA in both genders (Table IV), suggesting that JSN was more closely associated with the pain than osteophytosis. On the other hand, approximately 10% of men and 20% of women without radiographic knee OA ($KL = 0/1$) had knee pain. Although the prevalence of knee pain and radiographic OA with pain was approximately double in women what it was in men (Table II), the association of knee pain with radiographic knee OA, especially with $KL \geq 3$ OA, was stronger in men (Table IV). Furthermore, the odds ratio for knee pain of women compared with men in the subgroup without radiographic knee OA ($KL = 0/1$) was comparable to or greater than that in those with radiographic knee OA (Supplementary Table SI). This suggests the existence of a cause of pain that is independent of OA in women, while the pain in men may be more dependent on JSN by OA. Radiographic JSN represents not only joint cartilage destruction, but also meniscal loss or extrusion. In addition, knee pain may arise from a variety of structures other than joint cartilage, like menisci, synovium, ligaments, bursae, bone and the bone marrow[32–36]. Hence, comprehensive mechanistic studies for the knee pain taking various tissues in and around the knee joint into consideration will be needed to elucidate the relationship between radiographic OA and symptomatic OA.

Although the prevalence of radiographic knee OA increased with age in both genders, that of knee pain was age-dependent only in women (Fig. 1). This might be due to the accumulated mechanical stress to the knee due to the Japanese traditional lifestyle and the decreased muscle strength as described above, both of which women may experience more than men. Alternatively, elderly men generally retire from their occupations around 60 to 70 years, while women must continue to do household chores even after the age of 70.

There are several limitations in this study. First, the radiographic investigators did not have readers calibrate themselves to readings from other studies. Although we reported higher prevalence of radiographic knee OA than in previous studies, radiographic acquisition, scoring techniques and methodology across studies limit strict comparisons between our results and previous reports. Differences across studies in the thresholds used by readers to define osteophytes may have a substantial impact on their prevalence. The high prevalence of knee OA in our study compared to that in other populations may be due to such differences. Second, our analysis did not include patellofemoral joint radiographs, which would likely increase the prevalence of radiographic outcomes and perhaps increase the concordance between radiographic knee OA and its pain. Third, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with JSN but no osteophytosis. The investigation of the relationship among knee OA features including JSN and osteophytosis is the next task in the ROAD study.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic knee OA in the Japanese elderly. Knee pain was more strongly associated with $KL \geq 3$ OA with JSN than with $KL = 2$ with osteophytosis, although it was distinctly associated with radiographic OA between genders. Further progress in developing an accurate method for surrogate measurement of the structural severity of knee OA, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA and its relation to knee pain.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

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Supplementary material

Supplementary material for this article may be found, in the online version, at doi:10.1016/j.joca.2009.04.005.

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Differential Effects of Culture-expanded Bone Marrow Cells on the Regeneration of Bone Between the Femoral and the Tibial Lengthenings

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Background: Transplantation of culture-expanded bone marrow cells (BMC) and platelet-rich plasma (PRP) during limb lengthening shorten the treatment period by accelerating callus formation, but the direct effects of BMC and PRP on the regeneration of the bone have not been determined.

Methods: Fifty-one bones (23 femora, 28 tibiae) in 28 patients (17 males, 11 females), with an average age of 15.0 ± 3.21 years, were lengthened by treatment with BMC and PRP. Clinical outcome was compared between the 51 bones with BMC and PRP treatment and the 60 bones without cell therapy. The parameters including age at surgery, length gained, healing index (HI), number of BMC, bone-specific alkaline phosphatase (BAP) activity of BMC, and PRP concentration, were compared between the femur and the tibia treated with BMC and PRP. Linear regression analysis was then performed to correlate the HI and other variables.

Results: The HI of the BMC and PRP groups was significantly lower than that of the control group. Average HI, amount of lengthening, number of BMC, BAP activity, and PRP concentration were 30.0 ± 6.72 days/cm, 8.10 ± 2.90 cm, 1.35 ± 0.56 × 10^7, 9.02 ± 3.98 U/L, and 2.4 ± 0.7 × 10^6 /UL, respectively. There were no significant differences in the length gained, the number and BAP activity of BMC, and the PRP concentration between the femur and the tibia. Femoral lengthening showed significantly faster healing than tibial lengthening, although the age at surgery was significantly older in femoral lengthening. A negative relationship between the HI and the length gained was observed in the tibia. In the femur, there was a negative linear relationship between the HI and the number and BAP activity of BMC, whereas no significant correlations were detected in the tibia.

Conclusions: In femoral lengthening, decrease in the HI was remarkable by BMC and PRP transplantation, and there was a progressive increase in bone healing as the number and the osteoblastic differentiation of transplanted BMC increased. Our results suggested that regionally varying bone-forming processes by cell transplantation might be related to local blood supply and soft tissue covering.

Level of Evidence: Therapeutic retrospective study, level III.

Key Words: limb lengthening, bone marrow cells, platelet-rich plasma, cell transplantation, osteoblastic differentiation

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Limb lengthening has been used for the treatment of bone loss after trauma, congenital deficiencies, or tumor resection. This technique allowed reconstructive surgeons not only to lengthen the limb but also to correct angular and rotational deformities simultaneously. The treatment period, however, is long, which results in higher rates of complications such as pin track infection, adjacent joint contractures, delayed consolidations, and fractures. Acceleration of callus formation is essential for limb lengthening to minimize the treatment period and reduce associated complications. Tissue engineering strategy, which consists of 3 essential components (application of osteogenic cells, osteoinductive factors, and a scaffold), has emerged as a possible alternative to accelerate bone regeneration at the distracted gap.

Bone marrow-derived mesenchymal stem cell (BMC) can be easily manipulated ex vivo and directed toward the osteogenic lineage if cultured in the presence of dexamethasone.[1] Platelet-rich plasma (PRP) contains several osteoinductive growth factors that enhance and accelerate bone regeneration pathways.[2] Moreover, PRP can be a suitable carrier for BMC transplantation because it coagulates immediately by an addition of thrombin and calcium. We have introduced a novel cell therapy of BMC and PRP transplantation in lower limb lengthenings.[3] Retrospective comparative studies with and without cell transplantation demonstrated that transplantation of culture-expanded BMC and PRP into the distracted callus shortened the treatment periods and reduced the associated complications by accelerating new bone regenerates.[4,5] Favorable clinical outcome was observed, especially in the femoral lengthening rather than the tibial lengthening by treatment with BMC and PRP although

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the effects of the transplanted cells on the regeneration of the bone have not been determined.

In this study, the clinical outcome of the 51 lower limb lengthenings treated with BMC and PRP was retrospectively reviewed and compared between the femur and the tibia. Various factors that may influence the outcome of this cell therapy, including the number of transplanted BMC, osteoblastic differentiation of BMC, and platelets concentration in PRP, were then statistically analyzed to determine the effect of cell transplantation on the regeneration of the bone.

METHODS

BMC and PRP Transplantation

The methods of BMC culture and PRP preparation have been described previously.[3] For the preparation of the autologous serum for in vitro culture, 200 mL of venous blood was drawn from the patient before surgery. Approximately 40 mL of bone marrow aspirates were collected from the iliac crest during surgery and harvested with sodium heparin and Dulbecco modified Eagle medium (Sigma, St Louis, MO) supplemented with penicillin-streptomycin (Invitrogen, Carlsbad, CA), 10% patients' serum, 10^{-7} mol/L dexamethasone (Sigma), 10 mmol/L β-glycerophosphate (Sigma), and 50 μg/mL ascorbic acid phosphate (Sigma). Mononuclear cell fractions were isolated and cultured in the differentiation medium for osteoblastic differentiation. When culture dishes became semiconfluent, the adherent cells were dissociated and suspended for continued passages. The third-passaged (P3) BMC cultured for nearly 3 weeks were used for transplantation. Before transplantation, the culture media were examined for contaminations of bacterium, fungus, mycoplasma, and pathological viruses such as hepatitis B, hepatitis C, and cytomegalovirus. For the evaluation of osteoblastic differentiation of BMC, the bone-specific alkaline phosphatase (BAP) activity of the culture medium in which the P3 cells were incubated for 3 days was measured using commercially available enzyme immunoassay (SRL Inc, Japan).

Colleting venous blood and preparation of PRP were commenced within 48 hours before transplantation for fear of a decline in platelet function and increased risk of serious complication from bacterial contamination. PRP was prepared from approximately 200 mL of venous blood according to the method of Marx et al.[6] After the second centrifugation, total amount of PRP was finally adjusted according to the number of injection sites (4 to 5 mL of PRP per injection) by removing the superficial plasma. Processed PRP was then stored with agitation at room temperature until transplantation. A sample of PRP was also used for the determination of platelet count after processing.

The transplantation technique of BMC and PRP has been described previously.[3] At the operating room, BMC were dissolved in a PRP, and 5000 U of human thrombin was mixed with 2 meq of calcium gluconate. Then, 2 18-G needles were inserted at the distracted callus face to face with each tip. Two milliliters of a thrombin-calcium mixture and 4 to 5 mL of a BMC and PRP solution were injected simultaneously into the callus so that the PRP gel might develop within the injected site.

Patients

After the approval of the Institutional Review Board of Nagoya University Hospital in 2002, transplantation of BMC and PRP was performed in the patients who made a choice of this treatment, and provided written, informed consent according to the format of the Institutional Review Board. Inclusion criteria of this study were the patients who were lengthening the long bones with BMC and PRP transplantation and followed up at least 3 months after removal of the fixator. Indications for limb lengthening were the patients who have a limb length discrepancy over 3 cm or who are of stature shorter than −3 standard deviation secondary to skeletal dysplasias, congenital deficiencies, or endocrine conditions. The surgical technique and the distraction schedule were standardized in all patients. The proximal diaphyseal osteotomy was subcutaneously performed by multiple drill holes followed by an osteotome. After an initial delay (7 to 14 d), gradual distraction of 1 mm per day was commenced. The distraction rate was adjusted considering the callus formation on the radiographs and the range of movement of the adjacent joints. The physiotherapy regimen was also standardized in all patients. No postoperative immobilization was used and weightbearing with crutches was encouraged from the seventh postoperative day, depending on patient tolerance. For patients with a short stature, simultaneous lengthening of bilateral femora or bilateral tibiae was performed and BMC and PRP transplantation was done bilaterally. The decision to remove the fixator was made by at least 3 pediatric orthopaedists based on the radiologic appearance of the regenerated bone (continuity of at least 3 cortices with reformed medullary cavity).

Fifty-one bones in 28 patients were included in the study (Table 1). Twenty-three procedures were carried out in the femur and 28 in the tibia. There were 17 male and 11 female patients with an average age of 15.0 ± 3.21 years. Eleven had achondroplasia, 3 hypochondroplasia, 4 hormonal abnormalities, 4 other bone dysplasias, 3 longitudinal deficiencies (congenital pseudarthrosis of the tibia in 1, hemiatrophy in 1, and scleroderma in 1, respectively), and 3 had posttraumatic growth arrest. Orthofix monolateral external fixator (Orthofix SRL, Verona, Italy) was used for 9 femora and 7 tibiae, DynaFix rail deformity system (EBI; Parsippany, NJ) for 12 femora and 19 tibiae, and EBI multiaxial correction system (EBI; Parsippany) for 2 femora and 2 tibiae. All of the corrections were done gradually. The total length gained was determined from the radiographs taken before the distraction and immediately after removal of the fixator, and adjusted for the effect of magnification. The healing index (HI), which was calculated by dividing the entire external fixation time (d) by the extent of lengthening (cm), was then measured. The clinical outcome of the

TABLE 1. Details of the 51 Lengthened Bones Treated With Culture-expanded Bone Marrow Cells and Platelet-rich Plasma

Case	Age at Surgery (y)	Diagnosis	Fixator	Bone	Length Gained (cm)	HI (d/cm)	No. BMC (×10^7^)	BAP (U/L)	Platelets in PRP (/μL)	Correction
1	15	Achondroplasia	Orthofix	F	10.0	23.0	0.9	6.05	NA	−
	15	Achondroplasia	Orthofix	F	10.0	23.0	0.9	6.05	NA	−
2	14	Congenital longitudinal deficiency	Orthofix	F	3.6	26.9	1.8	6.65	NA	−
3	13	Achondroplasia	Orthofix	T	10.0	23.3	1.6	4.1	NA	−
	13	Achondroplasia	Orthofix	T	10.0	18.8	1.6	4.1	NA	−
4	20	Posttraumatic growth arrest	Orthofix	T	4.5	37.6	2.8	4.7	NA	−
5	19	Achondroplasia	Orthofix	F	9.0	18.2	1.1	7.5	NA	−
	19	Achondroplasia	Orthofix	F	9.0	20.9	1.1	7.5	NA	−
6	20	Achondroplasia	Orthofix	F	7.5	29.3	1.4	12.0	NA	−
	20	Achondroplasia	Orthofix	F	7.5	29.3	2.1	12.0	NA	−
7	20	Achondroplasia	Orthofix	F	8.2	18.7	2.1	13.5	NA	−
	20	Achondroplasia	Orthofix	F	8.8	21.6	3.2	13.5	NA	−
8	18	Hypochondroplasia	Orthofix	T	8.7	32.9	3.2	4.5	NA	−
	18	Hypochondroplasia	Orthofix	T	8.7	37.6	1.6	4.5	NA	−
9	16	Achondroplasia	Orthofix	T	8.0	28.5	1.6	9.2	NA	−
	16	Achondroplasia	Orthofix	T	8.0	37.6	1.6	9.2	NA	−
10	14	Metaphyseal dysplasia	EBI (rail)	T	6.5	37.4	2.6	10.9	NA	+
	14	Metaphyseal dysplasia	EBI (rail)	T	6.5	40.6	2.6	10.9	NA	+
11	14	Achondroplasia	EBI (rail)	F	9.6	22.7	1.1	13.6	NA	−
	14	Achondroplasia	EBI (rail)	F	9.6	22.7	1.1	13.6	NA	−
12	13	Mesomelic dysplasia	EBI (rail)	T	6.0	32.5	1.9	18	2,233,000	+
	13	Mesomelic dysplasia	EBI (rail)	T	6.0	37.2	1.9	18	2,233,000	+
13	12	Congenital longitudinal deficiency	EBI (rail)	F	3.3	35.8	0.8	3.7	2,422,000	−
	12	Congenital longitudinal deficiency	EBI (rail)	T	3.3	35.8	0.8	3.7	2,422,000	−
14	18	Hypochondroplasia	EBI (rail)	T	8.8	39.7	0.7	7.6	2,030,000	+
	18	Hypochondroplasia	EBI (rail)	T	8.8	39.7	0.7	7.6	2,030,000	+
15	13	Hormonal abnormalities	EBI (rail)	T	8.5	24.6	0.8	9.1	2,984,000	−
	13	Hormonal abnormalities	EBI (rail)	T	8.5	26.2	0.8	9.1	2,984,000	−
16	11	Achondroplasia	EBI (rail)	T	8.8	35.7	1.8	7.3	3,541,000	+
	11	Achondroplasia	EBI (rail)	T	8.8	31.7	1.8	7.3	3,541,000	+
17	19	Hypochondroplasia	EBI (rail)	F	6.5	24.6	1.3	5.7	2,812,000	−
	19	Hypochondroplasia	EBI (rail)	F	6.5	24.6	1.0	5.7	2,812,000	−
18	13	Achondroplasia	EBI (rail)	T	12.0	22.7	1.0	7.5	2,210,000	+
	13	Achondroplasia	EBI (rail)	T	12.0	24.4	1.4	7.5	2,210,000	+
19	12	Spondylometaphyseal dysplasia	EBI (MAC)	T	7.0	38.4	1.4	8.7	NA	+
	12	Spondylometaphyseal dysplasia	EBI (MAC)	T	7.0	38.4	1.4	8.7	NA	+
20	16	Achondroplasia	EBI (rail)	T	12.0	29.7	1.4	5.8	608,000	+
	16	Achondroplasia	EBI (rail)	T	12.0	27.3	1.4	5.8	608,000	+
21	14	Hormonal abnormalities	EBI (rail)	F	9.0	36.4	0.3	7.4	4,850,000	+
	14	Hormonal abnormalities	EBI (rail)	F	9.0	38	0.3	7.4	4,850,000	+
22	7	Congenital longitudinal deficiency	EBI (rail)	F	10.2	23.3	0.8	7.9	2,028,000	−
23	15	Hormonal abnormalities	EBI (rail)	T	6.0	40.5	1.2	11.5	2,316,000	−
	15	Hormonal abnormalities	EBI (rail)	T	6.0	40.5	1.2	11.5	2,316,000	−
24	10	Hormonal abnormalities	EBI (rail)	T	7.5	28.8	1.15	18.7	1,628,000	−
	10	Hormonal abnormalities	EBI (rail)	T	7.5	28.8	1.15	18.7	1,628,000	−
25	19	Achondroplasia	EBI (rail)	F	9.0	29.3	1.2	8.4	1,684,000	−
	19	Achondroplasia	EBI (rail)	F	8.7	30.3	1.2	8.4	1,684,000	−
26	19	Posttraumatic growth arrest	EBI (rail)	F	9.0	31.2	0.7	9	2,785,000	−
27	13	Spondylometaphyseal dysplasia	EBI (MAC)	F	5.5	25.1	1.4	13.4	2,740,000	+
	13	Spondylometaphyseal dysplasia	EBI (MAC)	F	6.0	25.3	1.4	13.4	2,740,000	+
28	12	Posttraumatic growth arrest	EBI (rail)	F	10.0	30.8	1.2	8.2	3,202,000	−

BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; F, femur; HI, healing index; NA, not available because of lack of data; PRP, platelet-rich plasma; T, tibia.

60 bones in 29 patients that were lengthened without additional cell therapy was reviewed as controls.

Statistical Analysis

The clinical values of age at surgery, amount of lengthening, the HI, number of transplanted BMC, BAP activity of BMC, and platelets concentration in PRP were shown as the average ± standard deviation. Differences in the outcome variables between the treatment groups were statistically analyzed by the Mann-Whitney U test for nonparametric data. As the HI between the femur and the tibia treated with BMC and PRP was different, lineal regression analysis was performed in the femur and the tibia separately to correlate the HI and other variables. Statistical significance was set at a P value of less than 0.05. Data analysis was performed using JMP version 6 (SAS Institute, Cary, NC).

RESULTS

Preoperatively intended lengths were obtained in all segments and the average HI was 30.0 ± 6.72 days/cm. The average length gained was 8.10 ± 2.90 cm, which resulted in the average percentage of lengthening which was 35.3 ± 13.3% of the original bone length. The average number of BMC for transplantation was $1.35 \pm 0.56 \times 10^7$. BAP activity in the culture medium was averaged at 9.02 ± 3.98 U/L. Platelets concentration in PRP for transplantation was averaged at $2.4 \pm 0.7 \times 10^6/\mu L$. Simultaneous gradual correction of deformity was performed in 18 bones (14 tibiae and 4 femora). Superficial pin track infection was commonly observed, especially in the femoral lengthening but was successfully treated with oral antibiotics. Complications that required an additional treatment occurred in 6 bones. Four patients had a fracture after the removal of the fixation device, 3 of them were femoral fractures treated by skin traction and 1 was a tibial fracture treated by above-knee plaster cast immobilization. Two patients required subcutaneous osteotomy for early consolidation during femoral lengthening. Overall complications occurred at an average of 0.12 times per segment.

The average HI of the bones treated with BMC and PRP (30.0 ± 6.72 d/cm) was shown to be significantly lower than that of the bones without cell therapy (51.4 ± 26.5 d/cm) both in the femur ($P < 0.0001$) and in the tibia ($P = 0.0059$), although there was no significant difference in the age at surgery between the 2 groups (Table 2). A larger amount of lengthening was gained in the BMC and PRP groups ($P = 0.0114$).

The average HI of femoral lengthening (26.6 ± 5.46 d/cm) was significantly lower than that of tibial lengthening (32.7 ± 6.46 d/cm) ($P = 0.0013$), although the age at surgery was significantly older in femoral lengthening (16.1 ± 3.57) than in tibial lengthening (14.1 ± 2.63) ($P = 0.0162$) (Table 3). The average amount of lengthening was 8.07 ± 1.97 cm in the femur and 8.12 ± 2.22 cm in the tibia. The average number of transplanted BMC in the femoral and tibial lengthenings was $1.23 \pm 0.62 \times 10^7$ and $1.45 \pm 0.56 \times 10^7$, respectively. The BAP activity of BMC was averaged at 8.95 ± 3.38 in the femur and 9.08 ± 4.47 in the tibia. The platelets concentration in PRP after processing had an average of $2.55 \pm 0.49 \times 10^6$ in femoral lengthening and $2.21 \pm 0.82 \times 10^6$ in tibial lengthening. There were no significant differences in the increase in length, the number and the BAP activity of BMC, and the platelets concentration in PRP.

As femoral lengthening showed significantly faster healing than tibial lengthening by BMC and PRP transplantation, the effect of cell therapy on the regeneration of the bone was analyzed separately in the femur and the tibia. There was a negative relationship between the HI and the length gained in tibial lengthenings ($P = 0.0008$) (Table 4). Age at surgery and platelets

TABLE 3. Comparison of the Parameters Between the Femoral and the Tibial Lengthenings

	Femur (N = 23)	Tibia (N = 28)	P*
Age at surgery (y)	16.1 ± 3.57	14.1 ± 2.63	0.0162†
Length gained (cm)	8.07 ± 1.97	8.12 ± 2.22	0.4307
HI (d/cm)	26.6 ± 5.46	32.7 ± 6.46	0.0013†
No. BMC ($\times 10^7$)	1.23 ± 0.62	1.45 ± 0.56	0.0855
BAP (U/L)	8.95 ± 3.38	9.08 ± 4.47	0.8128
Platelets in PRP ($\times 10^3$/uL)	2551 ± 492	2207 ± 817	0.2062

*According to the Mann-Whitney U test.
†Statistically significant.
BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; HI, healing index; PRP, platelet-rich plasma.

TABLE 2. Comparison of the Parameters Between the 51 Bones With BMC and PRP Transplantation and 60 Bones Without Transplantation

	No. Bones		Age at Surgery (y)		Lengthening (cm)		Healing Index (d/cm)	
	BMC and PRP	Control	BMC and PRP	Control	BMC and PRP	Control	BMC and PRP	Control
Femur	23	25	16.1 ± 3.57 $P = 0.7389$	16.2 ± 4.61	8.07 ± 1.97 $P = 0.1259$	6.58 ± 3.03	26.6 ± 5.46 $P < 0.0001$*	53.4 ± 23.4
Tibia	28	35	14.1 ± 2.63 $P = 0.0386$	15.9 ± 3.58	8.12 ± 2.22 $P = 0.0394$*	6.43 ± 2.85	32.7 ± 6.46 $P = 0.0059$*	49.9 ± 28.7
Total	51	60	15.0 ± 3.21 $P = 0.2350$	16.1 ± 4.01	8.10 ± 2.90 $P = 0.0114$*	6.50 ± 2.90	30.0 ± 6.72 $P < 0.0001$*	51.4 ± 26.5

*Statistically significant.
BMC indicates bone marrow cells; PRP, platelet-rich plasma.

TABLE 4. Linear Regression Analysis of the Healing Index in Various Parameters

	Correlation Coefficient (r)		Significance Level (P)	
Parameter	Femur	Tibia	Femur	Tibia
Age at surgery (y)	−0.204	0.335	0.3527	0.0813
Length gained (cm)	−0.208	−0.608	0.3418	0.0008*
No. BMC	−0.451	0.053	0.0309*	0.7879
BAP activity	−0.425	0.136	0.0433*	0.4896
Platelets in PRP	0.129	0.115	0.6891	0.6596

*Statistically significance.

BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; PRP, platelet-rich plasma.

concentration in PRP did not correlate to the HI in both bones. No significant correlations were detected for the number and BAP activity of BMC in tibial lengthening. For femoral lengthening, on the other hand, there was a linear relationship between the HI and the number of BMC ($P = 0.0309$) and BAP activity (0.0433). As the number and osteoblastic differentiation of transplanted BMC increased, there was a progressive increase in bone healing in the femur (Figs. 1, 2).

DISCUSSION

Transplantation of culture expanded BMC and PRP during limb lengthening is easy to perform because BMC can be expanded and manipulated into osteoblastic lineage by culturing them in a differentiation medium, and PRP can be easily prepared from venous blood by centrifugation. Moreover, it is safe with a minimal side effect because both BMC and PRP are autologous, which are nontoxic and nonimmunoreactive. In this study, the outcome of lengthening with BMC and PRP transplantation was reviewed and statistically analyzed based on not only clinical variables but also characteristics of transplanted cells to evaluate the efficacy of this cell therapy. We have shown that this cell therapy provided favorable effects on new bone regenerates during limb lengthening; however, it is very expensive. For 1 patient, it costs more than US$2000 including personnel expenses, culture instruments and chemicals, contamination tests, and so on. A cost-benefit analysis of this treatment will be needed.

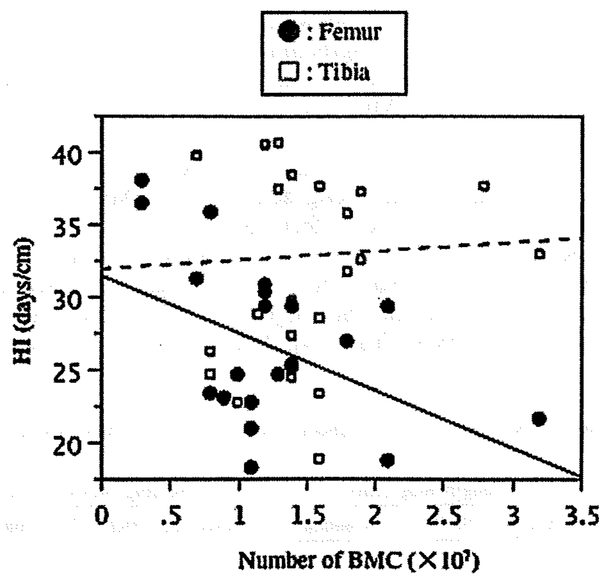

FIGURE 1. Linear regression analysis demonstrating the relationship between the healing index (HI) and the number of transplanted bone marrow cells (BMC). Significant negative correlation between the HI and the number of BMC was evident in the femur (solid line, $P = 0.0309$), whereas there was no correlation between them in the tibia (dashed line, $P = 0.7879$).

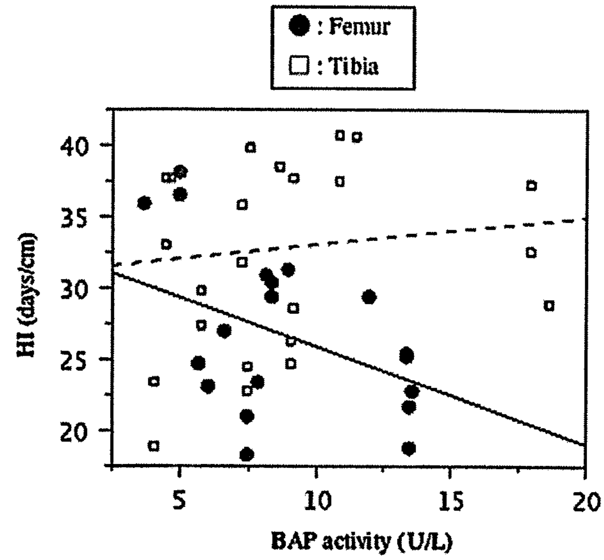

FIGURE 2. Linear regression analysis demonstrating the relationship between the healing index (HI) and the bone-specific alkaline phosphatase (BAP) activity of the transplanted bone marrow cells. Significant negative correlation between the HI and the BAP activity was evident in the femur (solid line, $P = 0.0433$), whereas there was no correlation between them in the tibia (dashed line, $P = 0.4894$).

Bone healing during limb lengthening depends on various parameters such as age at surgery and the amount of lengthening.[7–10] Generally, bone formation occurs more rapidly in younger patients. Several investigators reported a negative relationship between distraction length and healing time, which was evaluated by various parameters including HI, external fixation index, and distraction-consolidation index.[7,9,10] In this study, femoral lengthening showed faster healing than tibial lengthening irrespective of older age group and similar amount of length gained. However, there were no significant differences in the number of BMC, BAP activity, and PRP concentration between the femur and the tibia. These results suggested that the effect of BMC and PRP on the new bone regenerates might be related to the microenvironment at the transplanted sites.

The effect of an osteotomy site on new bone regenerates is controversial. Fischgrund et al[9] and

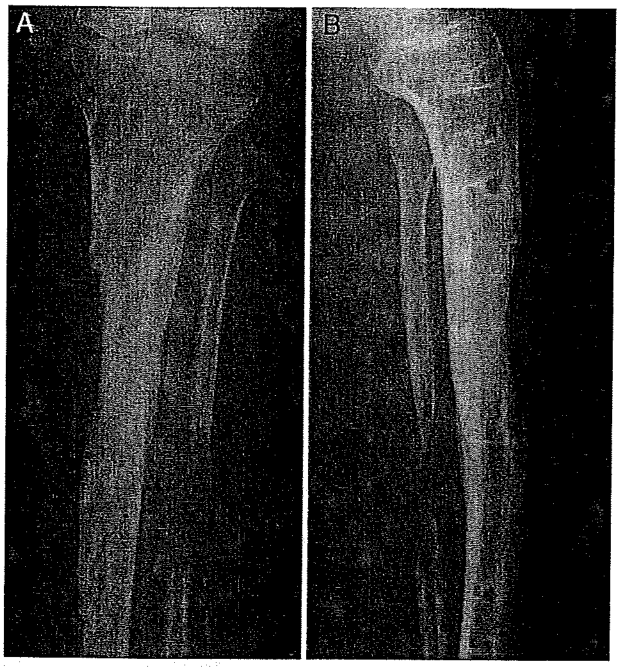

FIGURE 3. Anteroposteior (A) and lateral (B) radiographs of the left tibia of an 18-year-old man with hypochondroplasia (case 14) just after removal of the pins. Callus formation was predominant posterolaterally and extremely poor at the anteromedial aspect of the tibia.

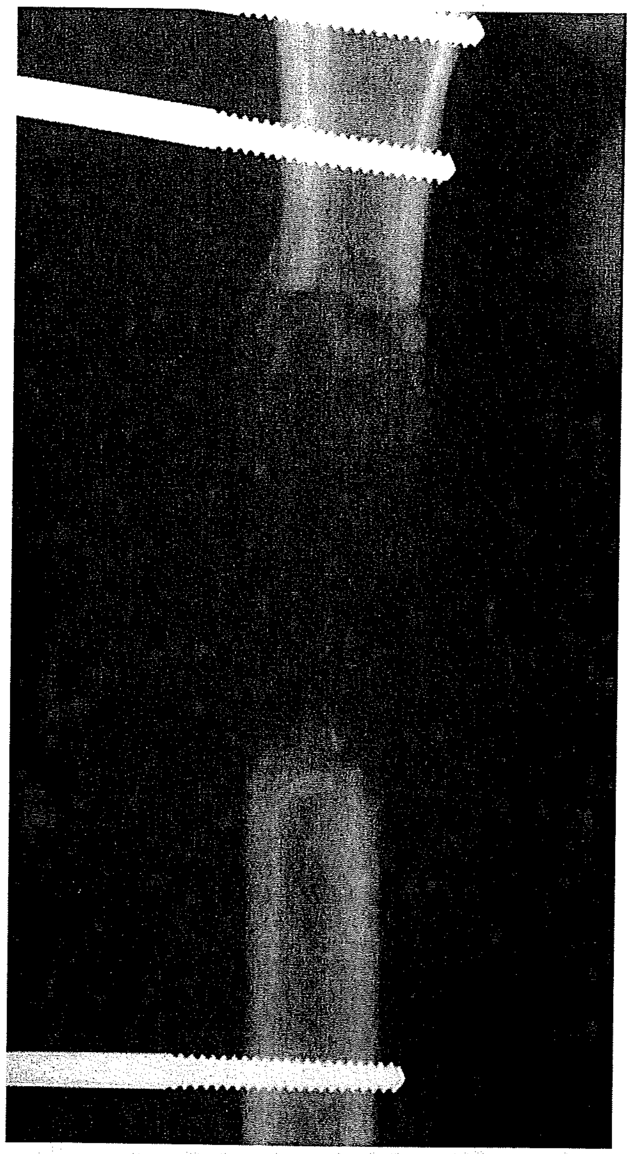

FIGURE 4. Anteroposterior radiograph of the right femur of a 19-year-old man with achondroplasia (case 5) just at the end of distraction demonstrating abundant fusiform-shaped callus formation.

Bonnard et al[11] reviewed limb lengthening procedures using the Ilizarov external fixator and noted faster bone healing in the femur than in the tibia. De Bastiani et al,[12] in contrast, reported that the HI was better for the tibia than for the femur in patients with achondroplasia whose bones were lengthened using the monolateral external fixator. Noonan et al[7] reviewed 261 limb lengthenings and documented that the healing time was relatively quicker in the femur than in the tibia but there were no significant differences in the adjusted HI between them. No significant differences in bone healing between the femur and the tibia were also reported in the studies by Donnan et al[13] and Fink et al.[14] Predominantly quicker healing in the femur may be due to the positive effect on osteogenesis of transplanted cells. For further clinical application of BMC and PRP therapy, it is necessary to determine the optimization of BMC and PRP conditions for transplantation.

Dallari et al[15] reported that a combination of BMC and PRP permits an acceleration in bone healing and bone remodeling processes in a rabbit model of bone defect. Lucarelli et al[16] stated that the proliferation of BMC promoted by 10% PRP but suppressed by high PRP concentration. The authors recently showed that a high platelet concentration in PRP in combination with BMC could accelerate the formation of new bone in the rat mode of limb lengthening.[17] In this study, the volume of extracted venous blood was standardized and the total amount of PRP was finally concentrated by removing the superficial plasma, which consequently resulted in a maximal platelets concentration in PRP. Lack of correlations between the HI and PRP concentration may be due to relatively constant platelets concentration in all but 1 patient (case 20) who could not obtain maximally concentrated PRP as a result of technical failure.

In vitro expansion of BMC offers the potential to generate a large number of osteoprogenitor cells; however, osteoblastic differentiation of BMC decreases after an expansion by several passages.[18,19] Several experimental studies showed that in vitro osteoblastic differentiation of BMC correlated with in vivo osteogenesis when these cells were transplanted with appropriate scaffolds.[18,20,21] The volume of extracted marrow samples was standardized in our protocol whereas the number of cells for transplantation, which depended on the number of available BMC after ex vivo expansion, ranged from 3.0×10^6 to 3.2×10^7. Osteoblastic differentiation of culture expanded BMC, which also depended on individual samples and ranged from 3.7 to 18.7 U/L. In the tibia, the number and the osteoblastic differentiation of BMC did not correlate with healing, and callus formation was predominant posterolaterally and poor at the anteromedial aspect of the tibia (Figs. 3A, B). In femoral lengthening, in contrast, there was a progressive increase in bone healing as the number and the osteoblastic differentiation of BMC increased, and abundant external callus was commonly observed after cell transplantation (Fig. 4). These results suggested the crucial significance in the adequate local blood supply for bone regeneration in BMC and PRP treatment. Lucarelli et al[22] noted that the transplantation of BMC and PRP improved bone repair by accelerating vascular invasion. BMC and PRP may not only promote osteogenesis at the transplanted site but may also contribute to vascular invasion and stimulate osteoprogenitor cells that are thought to reside in the surrounding soft tissues. Regionally varying bone-forming processes by cell transplantation might be related to local blood supply and soft tissue covering. Favorable effects on bone regeneration by BMC and PRP therapy could be expected when the cells are transplanted into the area with sufficient blood supply and abundant soft tissues.

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ORIGINAL ARTICLE

Radiographic Analysis of Movements of the Acetabulum and the Femoral Head After Salter Innominate Osteotomy

Hiroshi Kitoh, MD, Hiroshi Kaneko, MD, and Naoki Ishiguro, MD

Background: Salter innominate osteotomy (SIO) is widely used to improve the coverage of the femoral head in dysplastic acetabulum, but the geometric change after osteotomy and its effect on the outcome have not been well elucidated.

Methods: Pelvic radiographs of the 90 hips in 86 patients who underwent SIO for the treatment of acetabular dysplasia were reviewed and the movement of the distal fragment and the shift of the femoral head after SIO were analyzed. On the basis of the anteroposterior radiographs of the pelvis in a supine position taken at 5 weeks after operation, various parameters including an open-wedged angle at the osteotomy site (lateral rotation angle, LRA), lateral displacement of the distal fragment (distance *d*), and the ratio of the bilateral obturator foramen heights (the ratio of obturator heights, ROH), were measured. Improvement in the center-edge angle (CEA) and acetabular index (AI) after SIO was correlated with the LRA, distance *d*, and ROH. Horizontal and vertical distances from the pubic symphysis to the center of the femoral head were also measured from preoperative and postoperative pelvic radiographs and changes in the position of the femoral head were calculated. For the patients who were followed until skeletal maturity, final radiographic results were also assessed according to the Severin classification.

Results: The average improvement of the CEA and AI after SIO was 19.6 and 13.3 degrees, respectively. The average value of the LRA, distance *d*, and ROH were 30.2 degrees, 4.07 mm, and 73.0%, respectively. The LRA and distance *d* positively and the ROH negatively correlated with the improvement of the CEA and AI. The center of the femoral head moved an average of 7.06 mm caudally and 3.11 mm medially after SIO. Thirty-six hips (40%) in 36 patients were available for follow-up until skeletal maturity. The radiographic outcome was good (Severin I or II) in 33 hips and poor (Severin III) in 3 hips. Preoperative CEA was relatively smaller in a poor group. Greater improvement of the CEA during postoperative follow-up was observed in a good group.

Conclusions: Favorable coverage of the femoral head was obtained after SIO by shifting the center of the femoral head caudally and medially as well as rotating the distal fragment anterolaterally. SIO is a very effective procedure in improvement of the dysplastic acetabulum for the hips with round and spherical femoral head.

Level of Evidence: Therapeutic studies, level III (retrospective study).

Key Words: Salter innominate osteotomy, radiographic analysis, acetabular dysplasia

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Salter innominate osteotomy (SIO) has been the most commonly used procedure for treating acetabular dysplasia and residual subluxation in developmental dysplasia of the hip. Excellent or good results have been reported after SIO, but geometric changes of the acetabulum after SIO are not fully delineated.[1–3] The acetabulum is redirected by rotating the distal fragment anterolaterally to establish a larger weight-bearing area.[4,5] This acetabular movement takes place around an axis from the symphysis pubis to the site of the osteotomy, which results in an apparent deformity of the obturator foramen. Lateral rotation of the distal fragment could be measured by an angle of wedged bone graft placed into the resultant defect, and anterior torsion could be identified as a decrease in the height of the obturator foramen on anteroposterior (AP) radiographs of the pelvis.[6]

SIO not only increases the weight-bearing area of the acetabulum but also changes the moment of forces acting on the hip joint by shifting the center of the femoral head. Although medial shift of the femoral head would be beneficial for the hip by decreasing the moment of the forces, a lateral shift would be detrimental. The effect of SIO on the position of the femoral head, however, is still conflicting.[7–11] Changes in the position of the femoral head by SIO requires elucidation to understand the biomechanical effects of this procedure.

The effectiveness of SIO is radiographically judged by an increase in the center-edge angle (CEA) and decrease in acetabular index (AI) after operation. There is consensus on the importance of a lateral coverage of the femoral head, but differences in the amount of improvement of these parameters after SIO have been reported.[3,12–14] The reason for this difference is not clear, but it is possible that the degree of the distal fragment movement and the osteotomy technique influences the improvement of the parameters.

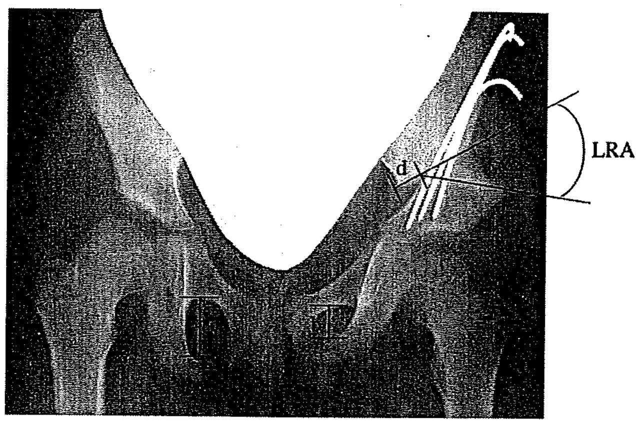
In this retrospective study, the movement of the distal fragment and the shift of the center of the femoral head by SIO were radiographically assessed for the patients who were treated with this procedure in our institution. Relationships were statistically analyzed between the degree of movement of the distal fragment and the improvement of radiographic parameters including the CEA and AI, which may lead to a better understanding of the geometry of this surgical procedure. In addition, middle-term results of the SIO for the correction of dysplastic acetabulum were analyzed in the cases that were followed until skeletal maturity.

METHODS

Between 1991 and 2008, SIO were performed in 120 consecutive patients for the treatment of dysplastic acetabulum. Two patients with significant neuromuscular diseases, 15 patients who were lost to follow-up, and 10 patients who underwent simultaneous derotational varus femoral osteotomy or open reduction in association with SIO were excluded in this study. Seven patients were also excluded because their femoral heads were so deformed (Kalamchi-MacEwen classification[15] grade III or more) that the center of the femoral head could not be identified based on the pelvic radiographs. Thus, 90 hips in 86 patients, 4 patients (8 hips) receiving bilateral and 82 patients (the left side was treated in 53 hips and the right side in 29 hips) receiving unilateral treatment, were included in this study. Nine hips in 8 boys and 81 hips in 78 girls were treated. The average age of the patients at the time of surgery was 5.79 ± 0.59 years. The average duration of follow-up after surgery was 5.11 ± 2.57 years. Ten hips of the 8 patients had not been treated before this surgery. The other 80 hips had undergone treatment for developmental dysplasia of the hip earlier and showed residual acetabular dysplasia at the time of the index surgery. Nineteen hips were reduced successfully by the Pavlik harness, and 57 hips were treated by overhead traction. Conservative treatment was unsuccessful in 4 hips and they were treated by open reduction before SIO.

Our criteria for SIO, usually at the age of 5 or 6 years, are AI of 30 degrees or more or CEA of 5 degrees or less.[16] The innominate osteotomy was performed following the guidelines set by Salter,[4] except that tenotomy of the iliopsoas and adductor longus muscle was not performed. The maneuver described by Wedge and Salter[17] was used to open the osteotomy, and the cortical iliac bone graft was obtained from the iliac crest and fixed with 3 threaded Kirschner wires. SIO was always performed as an isolated procedure in this study. The child was managed with a single-leg hip spica cast for 5 weeks with the hip in approximately 30 degrees of flexion and abduction.

AP radiographs of the pelvis were routinely taken in a supine position with the hips in neutral before operation and at 5 weeks postoperatively when the cast was removed. Regular review has continued with special reference to the callus formation of the osteotomy site and remodeling of the distal fragment. The AI and CEA were determined preoperatively and 5 weeks postoperatively. The most lateral point of the subchondral bone condensation in the acetabular roof (sourcil) was used as the landmark for the CEA and AI measurements. On the basis of the AP radiographs of the pelvis taken at 5 weeks after operation (just after cast removal), the following parameters were measured to evaluate the amount of movement of the distal fragment after SIO (Fig. 1). Lateral rotation angle (LRA) was defined as an open-wedged angle between the 2 fragments. Distance *d* (mm) was defines as lateral displacement of the distal fragment (positive values indicate lateral displacement and negative values indicate medial displacement). Changes in the heights of the obturator foramen after SIO (ratio of the obturator height, ROH) were calculated by the ratio of the maximum heights of bilateral foramens. Movement in the center of the femoral head was calculated from preoperative and 5 weeks postoperative radiographs of the pelvis. A Mose template was used to locate the centers of the femoral heads and their diameters were recorded. All measurements were corrected for changing magnification using the ratio of the diameters of the femoral heads on different films. The vertical and horizontal distances of the center of the femoral head from the center of the pubic symphysis were measured based on the preoperative and postoperative radiographs, and the shift of the femoral head after SIO was calculated (positive values indicate caudal or medial displacement and negative values indicate cranial or lateral displacement). For patients with skeletal maturity, radiographic results were evaluated according to the criteria proposed by Severin,[18] and were classified into 2 groups: a good group (Severin classes I and II) and a poor group (Severin classes III or more).



ratio of the obturator height (ROH) : b/c×100 (%)

FIGURE 1. Lateral rotation angle (LRA) was defined as an open-wedged angle at the osteotomy site. Distance (*d*) was defined as lateral displacement of the distal fragment (mm). The maximum obturator foramen heights of the operated side (*b*) and the unoperated side (*c*) were measured and the ratio of the obturator height (ROH) was calculated (%).

The measured values of the CEA, AI, LRA, distance *d*, ROH, and a shift of the center of the femoral head were shown as the average ± SD. The degree of the radiographic improvement of the CEA and AI after SIO was calculated from the preoperative and postoperative AP radiographs of the pelvis, and correlated with the variables representing distal fragment movements after operation (LRA, distance *d*, and ROH) using lineal regression analysis. The Mann-Whitney *U* test was used to determine the correlation between the average CEA and AI measurements and Severin's radiographic results at skeletal maturity. Statistical significance was set at a *P* value of less than 0.05. Data analysis was performed using JMP version 6 (SAS Institute, Cary, NC).

RESULTS

No major complications, such as postoperative avascular necrosis, nerve palsy, flexion contracture of the hip, or deep infection, occurred in our series. None had undergone additional procedures after the index surgery. The lateral displacement of the distal fragment was intraoperatively confirmed in all hips using image intensifier, but secondary loss of correction (medial displacement) was observed in 10 hips (11.1%) at the time of cast removal. Preoperative average CEA and AI were −0.86 ± 5.53 degrees and 34.0 ± 4.39 degrees, respectively. Postoperative CEA averaged 18.7 ± 5.97 degrees and was operatively increased by 19.6 ± 5.70 degrees (range, 5 to 35 degrees). Postoperative AI averaged 20.7 ± 5.02 degrees and was reduced on an average by 13.3 ± 4.03 degrees (range, 4 to 25 degrees) (Table 1).

The average values of the LRA, distance *d*, and ROH were 30.2 ± 6.56 degrees (range, 16 to 47 degrees), 4.07 ± 3.26 mm (range, −6 to 12 mm), and 73.0 ± 15.7% (range, 32% to 114%), respectively. Lineal regression analysis showed that an increase in the CEA after SIO positively correlated with the LRA ($r = 0.32$, $P = 0.0020$) and distance *d* ($r = 0.23$, $P = 0.0277$), and negatively correlated with the ROH ($r = -0.42$, $P < 0.0001$). Similarly, a decrease in the AI after operation was strongly related with the LRA ($r = 0.54$, $P < 0.0001$), distance *d* ($r = 0.41$, $P < 0.0001$), and ROH ($r = -0.47$, $P < 0.0001$) (Table 2). The interrelationship among the LRA, distance *d*, and ROH is summarized in Table 3. There was a strong correlation between the distance *d* and the LRA ($r = 0.62$, $P < 0.0001$). The ROH correlated negatively with the distance *d* ($r = -0.35$, $P = 0.0008$) and the LRA ($r = -0.48$, $P < 0.0001$).

TABLE 1. Improvement of the CEA and AI After SIO

	Preoperative	Postoperative	Change
CEA (degrees)*	−0.86 ± 5.53	18.7 ± 5.97	19.6 ± 5.70
AI (degrees)*	34.0 ± 4.39	20.7 ± 5.02	13.3 ± 4.03

AI indicates acetabular index; CEA, center-edge angle; SIO, Salter innominate osteotomy.
*Average ± SD.

TABLE 2. Relationship Between Improvement of the Radiographic Parameters and Variables of the Distal Fragment Movement (LRA, Distance *d*, and ROH)

Variables	Correlation With Improvement of the CEA	Correlation With Improvement of the AI
LRA	$r = 0.32$ ($P = 0.0020$*)	$r = 0.54$ ($P < 0.0001$*)
Distance d	$r = 0.23$ ($P = 0.0277$*)	$r = 0.41$ ($P < 0.0001$*)
ROH	$r = -0.42$ ($P < 0.0001$*)	$r = -0.47$ ($P < 0.0001$*)

AI indicates acetabular index; CEA, center-edge angle; LRA, lateral rotation angle; ROH, ratio of the obturator height.
*Statistically significance.

The center of the femoral head moved caudally in all hips, and the average downward shift of the head was 7.06 ± 3.23 mm (range, 1 to 15 mm) after SIO. It moved medially to an average of 3.11 ± 3.22 mm (range, −5 to 14 mm). The center of the femoral head horizontally remained unchanged in 9 hips, moved laterally in 9 hips, and moved medially in 72 hips (Fig. 2). There was a positive correlation between a caudal shift and a medial displacement of the femoral head after SIO ($r = 0.25$, $P = 0.0165$).

Thirty-six hips (40%) in 36 patients were available for follow-up after the patients had reached skeletal maturity. The preoperative and postoperative CEA averaged −0.36 ± 4.51 degrees and 18.4 ± 4.93 degrees, respectively. The CEA at the final examination averaged 26.4 ± 6.27 degrees and improved to 8.06 ± 6.52 degrees during postoperative follow-up (Fig. 3). The radiographic outcome was good (Severin I or II) in 33 hips (31 female and 2 male, the left side in 23 and right in 10) and poor (Severin III) in 3 hips (all were female, the left side in 2 and right in 1). The average age at operation was 5.89 ± 0.61 years in a good group and 6.33 ± 0.80 in a poor group, which was not statistically significant. Table 4 summarized the relationship between the final outcome and the radiographic parameters. The average preoperative CEA was −0.03 ± 4.38 degrees in a good group and −4.00 ± 5.20 degrees in a poor group. The postoperative CEA was averaged 18.7 ± 4.96 degrees in a good group and 14.7 ± 3.06 in a poor group. There were no significant differences in the preoperative and postoperative CEA between the 2 groups, although a good group tended to have better CEA. The average improvement of the CEA during postoperative follow-up was larger in a good group (8.76 ± 1.07 degrees) compared

TABLE 3. Interrelationship Among the Variables of the Distal Fragment Movement (LRA, Distance *d*, and ROH)

	Correlation Coefficient (*r*)	Significance Level (*P*)
Distance d vs. LRA	0.62	< 0.0001*
Distance d vs. ROH	−0.35	0.0008*
LRA vs. ROH	−0.48	< 0.0001*

LRA indicates lateral rotation angle; ROH, ratio of the obturator height.
*Statistically significance.

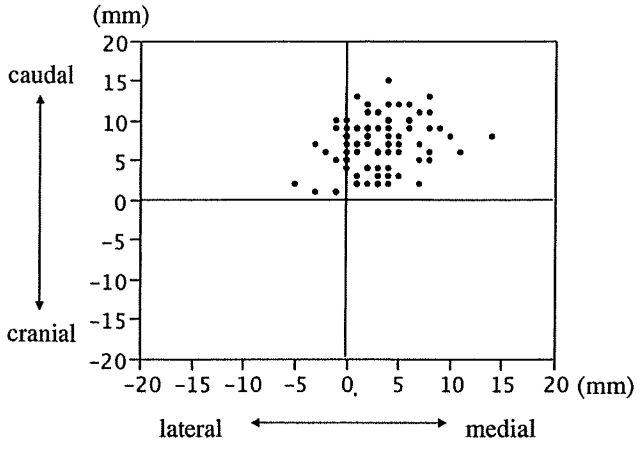


FIGURE 2. Scatterdiagram showing postoperative movement of the center of the femoral head. The femoral head moved an average of 7.06 ± 3.23 mm caudally and 3.11 ± 3.22 mm medially after Salter innominate osteotomy.

TABLE 4. Relationship Between the Radiographic Results and Average Measurements

Variables	Good Group (n = 33)	Poor Group (n = 3)	Significance*
CEA (degrees)†			
Preoperative	− 0.03 ± 4.38	− 4.00 ± 5.20	P = 0.1963
Postoperative	18.7 ± 4.96	14.7 ± 3.06	P = 0.1145
Final examination	27.5 ± 5.29	15.0 ± 5.29	P = 0.0049‡
Improvement during follow-up	8.76 ± 1.07	0.33 ± 6.11	P = 0.0543
AI (degrees)†			
Preoperative	33.2 ± 3.46	34.3 ± 2.89	P = 0.4166
Postoperative	20.4 ± 4.74	25.0 ± 3.00	P = 0.0898
Sharp angle (degrees)†			
Final examination	42.3 ± 3.14	47.3 ± 3.79	P = 0.0330‡

AI indicates acetabular index; CEA, center-edge angle.
*As determined by Mann-Whitney U test.
†Average ± SD.
‡Statistically significance.

with a poor group (0.33 ± 6.11 degrees), although differences were not statistically significant ($P = 0.0543$).

DISCUSSION

A favorable outcome after SIO in repairing the dysplatic acetabulum has been reported by many investigators,[1–5,12–14] but the factors influencing the effectiveness of this procedure have not been fully delineated. This study examined movements of the distal fragment and the femoral head by SIO that would affect the final outcome of this procedure. In our series, the average correction of the CEA (19.6 degrees) and the AI (13.3 degrees) obtained by SIO was within the range of correction reported in most studies.[2,7,13,19] The radiographic improvement was accompanied by movements of the distal fragment in approximately 30 degrees of lateral rotation, 4 mm of lateral displacement, and 30% decrease in the height of obturator foramen (Figs. 4A, B). The more the distal fragment moved, the better the femoral head was covered. With regard to the surgical technique, we pulled the distal fragment anterolaterally using the Charnley bone clamp after completion of the osteotomy by the Gigli saw, and then applied the maneuver technique so that the maximal anterolateral rotation of the fragment was achieved. As the distance d was correlated with the LRA and ROH, pulling out the distal fragment anterolaterally before the maneuver would be crucial in our surgical technique to obtain the maximal movement of the acetabulum.

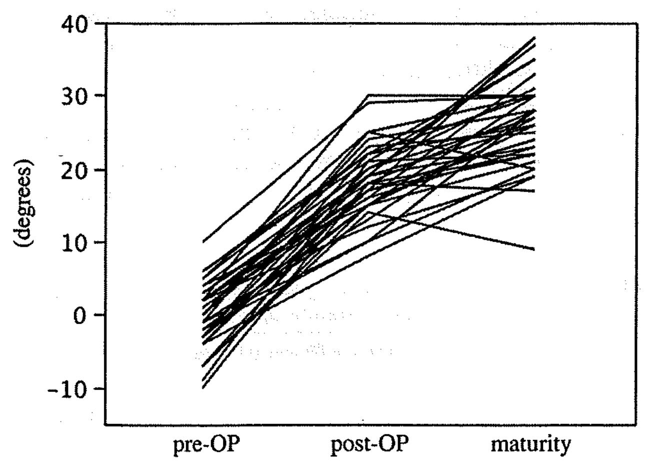


FIGURE 3. Sequential changes of the center-edge angle in 36 patients who were followed up until skeletal maturity.

The surgical technique described here is not the same that was described by Salter[4] with regard to omitting the adductor and the iliopsoas tenotomy. It may affect opening the osteotomy site and movement of the acetabulum, but we did not have difficulty in obtaining satisfactory correction in this study. Vengust et al[2] suggested that the acetabulum was not corrected to the maximum degree to eliminate the increase of the hip joint pressure when leaving the iliopsoas muscle intact. In our series, however, none has developed avascular necrosis or chondrolysis after SIO although the distal fragment was maximally opened by the maneuver technique without tenotomy of the iliopsoas muscle. Our study showed that tenotomy of the adductor and the iliopsoas muscle may be unnecessary in SIO for correcting the dysplastic acetabulum.

There are some limitations in this study because of the 2-dimensional measurements on a 3-dimensional object. Radiographic measurements of the hip joint will be affected by lumbar lordosis and the pelvic tilt in the sagittal plane. The hip spica casting frequently results in a decrease in the lumbar lordosis; thus, the accuracy of the radiographic assessments at 5 weeks postoperatively would be a concern. The LRA as measured from the AP radiographs does not accurately depict the true angle of the wedge, as the x-ray projection is oblique to the fragment. In this measurement technique, the LRA will be larger than the actual wedge.

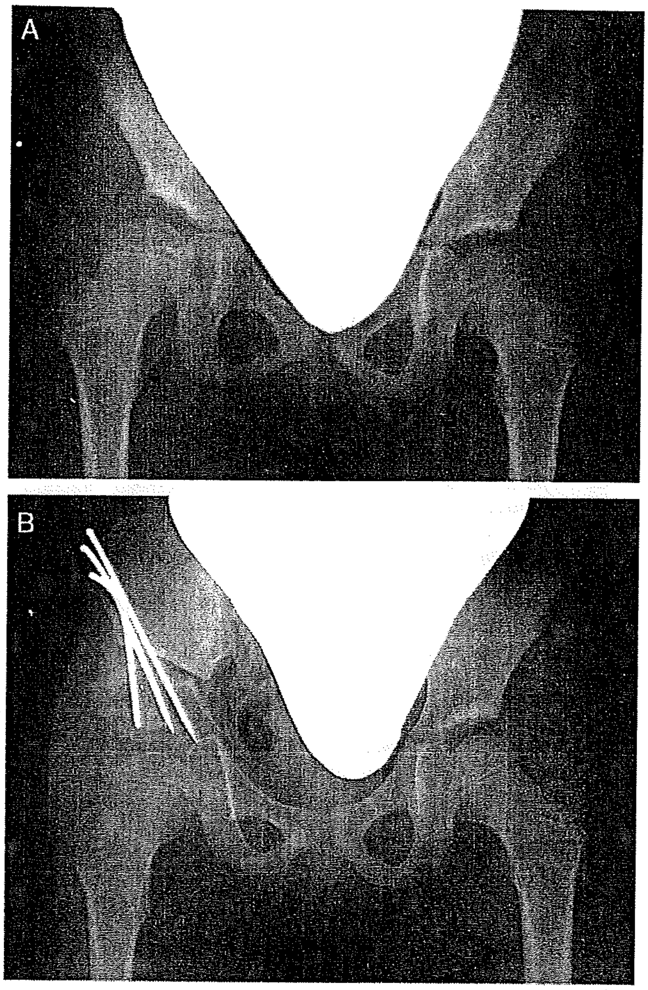


FIGURE 4. Anteroposterior radiographs of the pelvis of a 5-year-old girl with residual acetabular dysplasia of the right hip. Developmental dislocation of the right hip was conservatively reduced by overhead traction at the age of 10 months. Preoperative radiograph (A) indicated center-edge angle (CEA) of 1 degree, acetabular index (AI) of 33 degrees. Radiograph 5 weeks after surgery (B) showed CEA of 20 degrees and AI of 12 degrees. The distal fragment was rotated anterolaterally by the lateral rotation angle of 31 degrees, distance *d* of 6 mm, and the ratio of the obturator height of 67%. The center of the femoral head was moved 9 mm caudally and 3 mm medially after surgery.

Not only did the acetabulum moved to a more favorable position, but the center of the femoral head shifted an average of 7 mm caudally and 3 mm medially in this study. Earlier studies have shown that the femoral head moved caudally after SIO, but the horizontal movement of the head is still controversial.[7–11] Although the medial shift would be beneficial to the hip by decreasing the moment of the forces acting on the joint, the lateral shift would be detrimental. Utterback and MacEwen[7] discussed an increase in the distance from the body midline to the femoral head, but Radin and Paul[8] believed that SIO did not significantly alter the magnitude or direction of the resultant forces on the hip. Wong-Chung et al[9] reported the distance from the center of the femoral head to the body midline remained unchanged in 12, moved medially in 2, and moved laterally in 1 hip. They concluded that a correctly performed SIO does not significantly alter the distance from the center of the femoral head to the midline of the body. Rab[10] showed that the center of the hip joint moved 12 mm medially. Pfeifer et al[11] biomechanically showed that the hip joint was translated medially and caudally after SIO, and the length of gluteus medius and maximus muscle increased. They stated that the SIO leads to a reduction of hip joint and muscle forced in addition to increasing joint contact area. In this study, the center of the femoral head moved caudally in all cases and medially in the majority of cases after SIO, and correlations were observed between the downward shift and medial movements of the femoral head. Therefore, a correctly performed SIO increases the CEA and decreases the moment forces acting on the hip joint by displacing the distal fragment anterolaterally and shifting femoral head medially.

A similar percentage of the good radiographic results obtained after SIO has been reported by Gulman et al[13] (71% in 52 hips), Morin et al[14] (74% in 180 hips), Ito et al[3] (74% in 35 hips), and Vengust et al[2] (73% in 44 hips), although the classification as a normal hip at skeletal maturity varies among the studies. According to the radiographic criteria set by Severin,[18] we showed that 33 hips (91.7% in 36 hips) showed a good result at skeletal maturity. In this study, however, patients with aseptic necrosis of the femoral head established before the operation were excluded because accurate location of the center of the femoral head was difficult using a Mose template. Morin et al[14] and Ito et al[3] showed that preexisting necrosis of the femoral head made the prognosis for hips treated with SIO much less predictable. Excluding the hips with significant femoral head deformity may be a reason why this study showed better radiographic results than earlier reports.

The 3 hips that showed a poor result at skeletal maturity had a relatively smaller preoperative CEA and limited improvement of the acetabular development during postoperative follow-up. Vengust et al[20] reported that the average increase of the CEA during follow-up after SIO is smaller in the operated hips than in the contralateral nonoperated hips. They suggested that an unfavorable stress distribution is connected to the decrease of the CEA over time. The steep rise in the hip joint pressure after osteotomy could result in temporary impairment of acetabular development. As there were no significant differences in the degree of CEA improvement after operation between a good (19.0 degrees) and a poor group (18.7 degrees) in this study, we could not determine the reasons why some hips showed less improvement during postoperative follow-up. Overall, satisfactory Severin grade at skeletal maturity was achieved by SIO for the dysplastic acetabulum without femoral head deformities, although it does not always guarantee a good outcome in middle age. In conclusion, SIO is a very effective procedure for the dysplastic hips with round and spherical femoral head by rotating the distal fragment anterolaterally and shifting the femoral head caudally and medially.

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Predictive Factors for Unsuccessful Treatment of Developmental Dysplasia of the Hip by the Pavlik Harness

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Background: The Pavlik harness is a widely used and effective means of initial treatment of developmental dysplasia of the hip (DDH), but some hips fail to stabilize with the use of harness and avascular necrosis (AVN) of the femoral head can occur. Predictive factors for unsuccessful Pavlik harness treatment should be determined for appropriate indication of the treatment and prevention of AVN.

Methods: The outcome of Pavlik harness treatment for DDH was retrospectively examined in 221 hips of 210 patients who were treated initially at our institution and followed up for at least 1 year after the application of the harness. Univariate analysis was performed to determine predictors for failure of reduction and for the incidence of AVN by using the Mann-Whitney *U* test for continuous variables and the Fisher exact test or the Pearson test for categorical variables. Next, independent multivariate predictors for the failure of reduction and the incidence of AVN were identified using logistic regression analysis.

Results: One hundred and eighty-one hips were reduced and the overall rate of reduction was 81.9%. AVN that was diagnosed according to the criteria of Salter et al was identified in 16 of the 181 reduced hips and the rate of incidence of AVN was 8.8%. Bilaterality and decreased distance "*a*," as defined by Yamamuro and Chene, were statistically significant univariate and multivariate risk factors for the failure of reduction. Between them, distance *a* was the most powerful predictor. Adduction contracture of the hip (abduction with the hips flexed to 90 degrees < 60 degrees) was the only significant univariate and multivariate predictor for the incidence of AVN.

Conclusions: Distance *a* and adduction contracture of the hip were important predictors for the outcome of Pavlik harness treatment. We concluded that the Pavlik harness is a very safe and effective means of DDH treatment for the hips with abduction ≥ 60 degrees and distance *a* ≥ 6 mm.

Level of Evidence: Therapeutic studies, level III (retrospective study).

Key Words: developmental dysplasia of the hip, Pavlik harness, failure of reduction, avascular necrosis, predictive factors

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The Pavlik harness is a widely used and effective means of initial treatment of the developmental dysplasia of the hip (DDH) in patients under the age of 6 months.[1,2] It is considered to have a favorable rate of hip reduction and a low incidence of complications such as avascular necrosis (AVN) of the femoral head. On the basis of previous studies examining more than 100 DDH treated with the Pavlik harness, the reported rate of reduction ranges from 79% to 96% and the incidence of AVN from 0% to 22%.[3–13] Treatment with the harness, however, does not always provide a good result, as some hips fail to stabilize with the use of harness and AVN can occur. AVN is a serious iatrogenic complication and treatment is often unsatisfactory.[14] The vascular disturbance to the secondary epiphysis and the growth plate of the proximal femur leads to joint deformity, limb length discrepancy, and subsequent arthrosis. Greater effort should be made to prevent AVN in Pavlik harness treatment.

Predictive factors for unsuccessful Pavlik harness treatment (the hips that were unreduced or reduced followed by AVN) should be determined for appropriate indication of the treatment and prevention of AVN. Although several investigators have reported various predictors of treatment failure including male gender,[15] initial irreducibility,[16] bilateral dislocation,[10,16] severe dislocation,[5,9,10,17] and age at the time of Pavlik harness initiation,[7,9,16,18] it is still uncertain in the selection of patients for the harness and indications for abandoning the treatment. In conducting a retrospective study using univariable and multivariable analyses, we investigated the predictors that may contribute to incomplete reduction and the incidence of AVN for the patients with DDH treated at our institution. The purpose of this study was to determine the factors predictive for the outcome of the Pavlik harness treatment and to establish criteria for safe and effective application of this treatment.

METHODS

The Pavlik harness has routinely been used in our institution to treat infant hip subluxation and dislocation, but it has not been applied for hips with acetabular dysplasia without displacement of the proximal end of the femur. A dislocation was suspected clinically by limited abduction or shortening of the affected extremity, and a