

Table 2 Age-specific number and incidence of fractures after the first hip fracture

Age group (years)	n	Person (years)	Subsequent fractures						Incidence (per 1,000 person-years)			Rate ratio of hip fractures ^a
			Once	Twice	Total patients	Total fractures	Hip fractures	Clinical vertebral fractures	All fractures	Hip fractures	Clinical vertebral fractures	
65–74	276	275	15	2	17	19	10	3	69.0	36.3	10.9	18.6
75–84	919	906	59	2	61	63	26	15	69.6	28.7	16.6	3.3
85–94	1,025	1,003	62	3	65	68	36	7	67.8	35.9	7.0	1.5
≥95	108	106	10	0	10	10	5		94.8	47.4		1.9
Total	2,328	2,289	146	7	153	160	77	25	69.9	33.6	10.9	4.0

^a Age- and gender-specific incidences, reported previously for the general population in Japan, were adopted to compare the risk of hip fracture among patients with a first hip fracture

walk without difficulty,” “to walk outside with a walking aid,” and “to walk only inside with an aid” and “dependent” was “unable to walk without support” and “completely unable to walk.” The proportion of patients with subsequent fractures was significantly higher in the “dependent” than in the “no aid” ambulatory group. The proportion of patients with subsequent fractures was significantly higher among patients treated with antiosteoporosis drugs than those without antiosteoporosis drugs during the posthospitalization duration. There was no significant difference between the two groups regarding other factors. A multivariate analysis was performed using variants such as body weight and ambulatory abilities before the first hip fracture, and only body weight was a significant risk factor for subsequent fractures (OR = 0.96, 95% CI 0.928–0.993).

Discussion

This study demonstrated a high risk of subsequent fractures in patients with an initial hip fracture. It also revealed that, after fractures, antiosteoporosis pharmacotherapy was prescribed in only 19.6% of patients during their hospitalization and in only 18.7% during the 1-year follow-up period after discharge from the first hospital stay. The strength of this study is the substantially large number of subjects with a wide age distribution. As a result, the age-specific incidence of a second hip fracture in patients with an initial hip fracture could be calculated.

In retrospective studies, the rate of sustaining a second hip fracture is reported to be 7.5–11.8% [9–12]. In a population-based cohort study, Melton et al. [13] estimated that the recurrence rate for an additional hip fracture was 1% at 1 year after the first fracture in Minnesota in 1943–1977. Another US population-based study showed almost identical data, with a cumulative incidence of a second hip fracture of 2.3–2.5% after 1 year [2, 14], while the cumulative incidence after 5 years varied between 8.2

and 20%. A recent report from Finland showed a higher risk of 5.08% for persons aged 60 years and over within the first year following an initial fracture [15]. These differences may mirror the large variations in the risk of hip fractures and life expectancies in different populations.

Very little data are available on the risk of sustaining a second hip fracture after an initial hip fracture in the Asian population, although there is a large difference in the incidence of fragility fractures between Asians and Caucasians [1]. In a prospective study, Yamanashi et al. [16] reported that the annual incidence of a second hip fracture was 0.038 per person-year during the first year after an initial hip fracture and 0.028 per person-year during the second year. The 1-year incidence rate as determined in our current study (3.40%) is very consistent with their data. The age- and gender-specific incidence rates of sustaining a second hip fracture established in this study indicate that the rate ratio of a second hip fracture compared to the general population in Japan is higher in patients with an initial hip fracture under 75 years of age than that in those 75 years or older. In a Danish study, age- and gender-specific incidence rates (per 1,000 person-years) in women were 40, 51, 62, and 73 in the age groups 60–69, 70–79, 80–89, and ≥90 years, respectively [14]. Although the incidence rates of a second hip fracture in the Japanese and Caucasian populations are thought to be equal [16], there are differences in the population over 70 years of age, possibly due to a lower hip-fracture incidence in the Japanese population compared to that in northern Europe.

In this study, second hip fractures most frequently occurred within 32 weeks after the first hip fracture. The rate of sustaining a second hip fracture in a previous Japanese study tended to rise during the first 8 months after the first hip fracture and then to plateau [16]. A recent nationwide study in Denmark with a large number of hip-fracture patients demonstrated that the risk of a second hip fracture was increased almost 12 times at 1 month and more than doubled at 1 year; however, the risk remained significantly elevated until 15 years of follow-up [14].

These findings indicate that the early period of 6 months after the first fracture is a window of opportunity to execute a strategy for fracture prevention.

It has been reported that a previous fracture at any site is an important risk factor for future fractures [17]. Although the risk factors for hip fractures have been well defined in Caucasian subjects, only two epidemiological studies have examined risk factors for hip fractures in Japanese subjects [18, 19]. In the current study, body weight was a risk factor for a second hip fracture; however, age and other comorbidities were not associated with this risk. The study by Yamanashi et al. [16] demonstrated that senile dementia and Parkinson disease are important risk factors for second hip fractures and that prefracture ambulatory ability was similar between the unilateral and bilateral hip-fracture groups. A large cohort Danish study demonstrated that prior fractures, alcoholism, living alone, higher income, and advanced age are risk factors for second hip fractures [14]. Lonnroos et al. [15] found no significant risk of a second hip fracture with multiple comorbidities including dementia, whereas Berry et al. [2] reported a significantly increased risk in patients with a high level of functioning compared to those with moderate functioning. On the other hand, Chapurlat et al. [20] found that walking for exercise, which is an indirect marker for functional status, was a protective predictor. The explanation for these discrepancies might be caused by differences in the definition of comorbidity used in the various studies [14].

It is reported that the vast majority of patients who experience a hip fracture do not take antiosteoporotic therapy after the fracture [7, 8]. Among patients who begin antiresorptive osteoporosis treatment after fracture, the adherence to treatment decreases over time and remains suboptimal [8, 21]. Inadequate treatment after the first hip fracture became evident in the current study. In the current study we also found that patients undergoing osteoporotic therapy were more likely to sustain a new fracture than those not undergoing pharmacotherapy. This is probably due to the fact that more fractures occurred in those with severe osteoporosis; therefore, there was an increased likelihood of prescription of pharmacotherapy. It was not determined if prescribing antiosteoporosis drugs during the 1-year posthospitalization period was effective for fracture risk reduction. It is now known that oral bisphosphonate treatments for 3 years [22] or an annual infusion of zoledronic acid for 1.9 years [23] after repair of a hip fracture is associated with a reduction in the rate of new clinical fractures including hip fracture [22] as well as an improvement in survival [23].

There are some limitations to the current study. First, we estimated the risk of sustaining a second hip fracture based

on hospital records from the treating hospital and questionnaires from the patients and calculated rate ratios based on reported age-specific incidence rates derived from a different research method. Because mortality is increased after a hip fracture, this approach underestimates the true incidence and might lead to biased estimates. Although the mortality in this study was much lower than that reported previously, 304 patients were lost to follow-up and their true life span was unknown. Since further follow-up was difficult, this is a limitation of this study; therefore, the true mortality of this study must be interpreted with caution. Second, we included only female patients ≥ 65 years. It is well known that mortality and prognoses are poorer in male versus female patients, and this might affect our results. However, this effect would be limited since the number of female patients with a hip fracture is 3.8 times that of male patients in Japan [24]. Third, we collected data based on admission records and therefore could not fully eliminate patients with additional hip fractures treated at other hospitals. Each rural hospital from where our data originate is the main hospital in its region and has orthopedic specialists. Thus, most patients sustaining fractures visit these hospitals, and the number of patients with an additional hip fracture who are missed would be limited. However, the possible bias introduced by this would underestimate the fracture incidence. A lack of sufficient validation is a potential weakness. Unfortunately, we were not able to further validate our data. Finally, we could not compare the BMD between patients with and without a subsequent hip fracture since BMD was measured in only 314 patients. Although some reports have suggested that BMD between patients with and without an additional hip fracture was similar [10], another study showed that patients with a lower BMD are more likely to sustain an additional hip fracture [20].

In conclusion, the current study discovered a high risk of a subsequent fracture after an initial hip fracture and that the treatment for patients after the first hip fracture is not entirely adequate. Since hip-fracture patients are the most plausible candidates in the prevention of subsequent fractures, prescribing appropriate osteoporosis treatments is essential along with more aggressive interventions for preventing falls.

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2010年佐渡市における骨粗鬆症関連骨折発生調査

佐久間真由美^{1,2)} 生沼武男³⁾ 小熊雄二郎³⁾ 今尾寛太³⁾
 古賀 寛³⁾ 山岸健太郎³⁾ 宮坂 大²⁾ 田邊直仁⁴⁾
 遠藤直人²⁾

はじめに

わが国の高齢化は今後も進行し、2055年には高齢化率が40.5%に達すると予想されている。一方、骨折は介護必要とする原因において上位を占めており、高齢者の骨折を予防することは今後も重要な課題であると考えられる。

こうした背景において、骨折数の実態と推移を継続的に把握することは、今後の予防対策を考えるうえで必要である。これまでの経緯として、われわれは新潟県佐渡市(1島1市)において、2004年および2005年～2007年にわたり、骨粗鬆症関連骨折(大腿骨近位部、椎体、上肢)の発生調査を行ってきた。

1 目的

2010年の1年間の佐渡市における大腿骨近位部、椎体、上肢の骨折発生数を把握する。また、経年変化についても検討する。

2 対象

新潟県佐渡市は2010年10月現在、人口62,394人、高齢化率は36.8%(県の推定人口統計による)である。同市において調査を行った。同市においては高齢者の転出入は少ないと考えられる。

対象者の選択基準は以下のとおりである。

- ・2010年1月1日から12月31日の間に発生した骨折で医療機関を受診した患者
- ・年齢50歳以上の男女
- ・住所が佐渡市にあるもの

- ・骨折は大腿骨近位部骨折、椎体骨折、橈骨遠位骨折、上腕骨近位骨折の4種類
- ・腫瘍による病的骨折は除外する。

3 方法

調査を依頼した施設は、市内の整形外科を標榜する全施設、および椎体圧迫骨折の患者が受診する場合がある診療所で、4病院2医院に調査を依頼、回答を得た。特に大腿骨近位部骨折に関しては、ほぼ全例が市内のA総合病院に紹介される。調査協力施設にて受診した2010年1月1日から12月31日の間に発生した骨折症例で、すべての選択基準を満たす患者を担当医が登録する。

調査項目は、発生数、発生率、受傷平均年齢、受傷場所、受傷原因(大腿骨近位部骨折のみ)、過去6ヵ月の骨粗鬆症薬服薬の有無、骨折の既往であった。

調査は個人情報に留意し行った。調査計画については、新潟大学医学部倫理審査委員会の承認を得た。

4 結果

1) 発生数・発生率・受傷平均年齢

佐渡市内の同骨折発生数は大腿骨、椎体、橈骨、上腕骨の順に115, 191, 89, 23で椎体をもっとも多く、ついで大腿骨、橈骨、上腕骨の順であった。受傷平均年齢は、大腿骨84.4±9.51歳、椎体80.1±8.18歳、橈骨71.1±10.6歳、上腕骨82.6±9.9歳であった。

¹⁾ 新潟医療福祉大学医療技術学部理学療法学科, ²⁾ 新潟大学大学院医歯学総合研究科機能再建医学講座整形外科科学分野, ³⁾ 佐渡総合病院整形外科, ⁴⁾ 新潟県立大学人間生活学部健康栄養学科

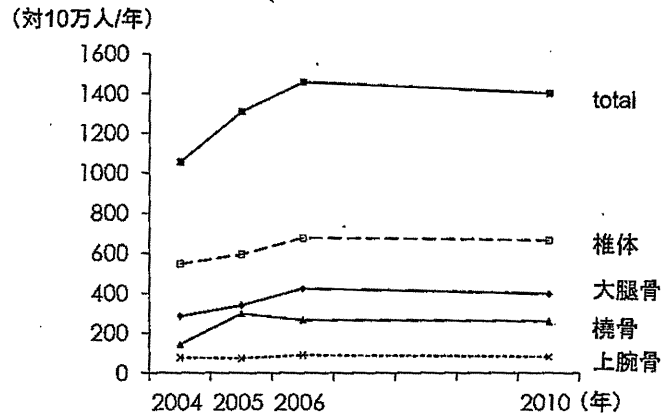


図1 発生率の推移 (60歳以上)

- ・2004～2006年の期間：特に椎体、大腿骨で発生率が上昇した。
- ・2006年と2010年の比較はほぼ横ばいであった。

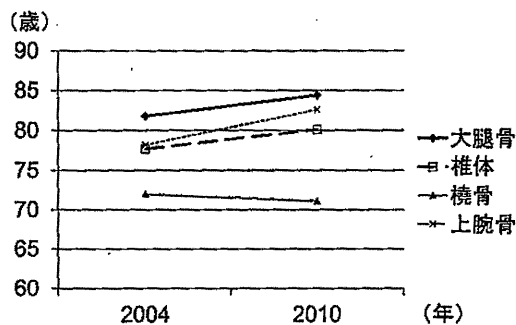


図2 受傷平均年齢の推移

- ・2004年に比べ、2010年は橈骨を除き受傷平均年齢が上昇した。

2) 発生数・発生率・受傷平均年齢の経年的推移

2004年との比較¹⁾では各骨折の発生率はおおむね上昇した。ただし、2006年と2010年の比較²⁾では、4種類の骨折とも発生数・発生率ともにほぼ横ばいで、著明な増加はみられなかった(図1)。

受傷平均年齢を2004年と比較すると、橈骨を除き平均年齢は2～4歳上昇した。橈骨では横ばいであった(図2)。

3) 受傷場所・要因

受傷場所は、橈骨で屋外での受傷が64%と過半数を超えたが、大腿骨、上腕骨では屋内での受傷が70%以上であった。椎体では不明との回答

が43%、ついで屋内、屋外の順であった。

大腿骨近位部骨折の受傷原因は転倒が72%で、転落と不明がこれにつぎ10%ずつであった。

4) 治療歴

過去6ヵ月以内の骨粗鬆症治療薬の内服状況は、いずれも服薬無との回答が大多数を占め、服薬有との回答は大腿骨7%、椎体13%であった。これは2004年の4% (大腿骨・椎体いずれも) よりもやや上昇していた。

5) 過去の骨折歴

過去の骨折については問診による調査であったが、4種類のいずれの骨折においても「骨折なし」との回答が過半数以上を占めた。大腿骨では過去の大腿骨近位部骨折の既往が13%と、過去の同部骨折としては最多であった。

5 考 察

4骨折全体では年間418骨折で、発生率は669.9(人口10万・年)であった。そのなかで椎体骨折がもっとも多かった。

発生数・発生率は2004年時との比較では上昇したが、2006年と2010年との比較では4骨折ともほぼ横ばいであった。2006年以降、増加が鈍化あるいは増加が止まっていることが示唆された。この理由は明らかではないが、欧米では骨吸収抑制剤の普及ですでに発生率が減少に転じた

との報告がみられている³⁾。佐渡市において減少とはいえないものの、一般的な骨粗鬆症に対する知識の普及や啓発・治療の効果がやや出てきた可能性も考えられる。しかし2006年と2010年の2点間のみの比較であるので、横ばいの傾向になっていると結論するにはまだ早急であると思われる。

受傷時平均年齢は、2004年との比較では橈骨を除き平均年齢が上昇した。人口の高齢化に伴い、高齢で骨折するケースが増加していると考えられ、高齢者骨折の継続的な予防対策が重要と考えられる。

受傷場所は、2004年時よりも屋内での骨折が増加傾向であった（大腿骨 2004年 69%→2010年 73%）¹⁾。

受傷原因は転倒が多く（72%）、2004年とほぼ同様であった。

骨粗鬆症治療薬の内服状況について、服薬有との回答は大腿骨 7%、椎体 13%であり、2004年のそれぞれ4%よりも上昇したが、まだ十分な状況であるとはいえない。ここからさらに内服率を向上させれば、骨折を減らせる可能性も示唆された。

過去の骨折については、大腿骨では13%が過去の大腿骨近位部骨折の既往があり、他の骨折に比べ最多であった。対側の骨折予防の強化は特に重要と考えられる。また、大腿骨では「骨折なし」との回答も橈骨について63%と高値であった。大腿骨では高齢、認知症の方も多く、問診では自身の骨折歴の把握が困難な可能性がある。このた

め、エックス線で既存椎体骨折を確認する場合とでは、過去の骨折既往の数値に差が出ると考えられる。

ま と め

骨折発生数・発生率は2004年から上昇傾向にあったが、2006年と2010年との比較では著明な上昇はみられなかった。受傷平均年齢は橈骨を除き2004年より上昇した。骨粗鬆症治療薬の服薬率は2004年より増加したが、依然服薬なしのケースが大多数であった。

今回の結果から導かれる骨折予防対策として、今後さらに骨折を減少させるためには、①特に高齢者の骨折予防対策、②大腿骨近位部骨折における対側骨折の予防、③服薬率の向上は重要であると考えられる。

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Prevalence and characteristics of unilateral knee osteoarthritis in a community sample of elderly Japanese: do fractures around the knee affect the pathogenesis of unilateral knee osteoarthritis?

Akinobu Nishimura · Masahiro Hasegawa · Hiroki Wakabayashi ·
Kakunoshin Yoshida · Ko Kato · Tomomi Yamada · Atsumasa Uchida ·
Akihiro Sudo

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Abstract

Background The purpose of this study was to investigate the prevalence and characteristics of unilateral knee osteoarthritis (KOA), to investigate what percent of contralateral healthy knees in patients with unilateral KOA progress to KOA, and to investigate whether knee fractures influence unilateral KOA.

Methods Studies were performed every two years from 1997 to 2009 in Miyagawa village, for a total of seven studies. A total of 1239 village inhabitants aged ≥ 65 years participated in these studies at least once. KOA was defined as a Kellgren–Lawrence (K/L) grade ≥ 2 . Based on the knee X-ray at the first examination, participants were divided into three groups: no KOA (N group), unilateral KOA (U group), and bilateral KOA (B group). The U group was divided into two subgroups: K/L grade II–I combination (II–I group), and the U group without the II–I combination (G>2 group). To investigate whether knee fractures influence unilateral KOA, the fracture history was considered.

Results The percentages of participants classified into the N, B, and U groups (II–I and G>2 group) were 68.4, 21.6, and 10.0 % (7.8 and 2.1 %), respectively. Most of the U

group had the II–I combination (78.7 %). The percentages of knee fractures in the N, B, II–I, and G>2 groups were 3.3, 5.3, 6.3, and 38.5 %, respectively. Overall, 49.2 % of the U group proceeded to bilateral KOA over an average of 5.3 years.

Conclusions The prevalences of definite radiographic bilateral and unilateral KOA were 21.6 and 10.0 %, respectively. Overall, 49.2 % of the participants with unilateral KOA developed KOA in the contralateral knee over an average of 5.3 years. If bilateral KOA advanced simultaneously, the II–I group was considered to represent the midpoint of progression to bilateral KOA. Bilateral KOA advanced simultaneously except in cases with a history of knee trauma, such as fractures.

Introduction

Osteoarthritis of the knee (KOA) is the most common form of arthritis leading to pain and loss of function in older adults [1]. It is well known that Japan has an aging population, and thus the prevalence of Japanese patients with KOA is increasing [2]. Several studies have described the prevalence of KOA as well as various risk factors and their associations with KOA [3–10]. However, in most previous studies, information on only one knee—the knee with the worst grade—was recorded. There have been only a few studies where each knee grade was recorded, meaning that the natural history of the contralateral knee is poorly understood [11, 12]. In clinical practice, patients with unilateral knee pain are frequently encountered. If only the knee with the worst grade is X-rayed, then the condition of the contralateral knee can only be assumed. For clinicians to treat KOA, it is important to know the prevalences of unilateral and bilateral KOA in order to satisfy both the

A. Nishimura (✉) · M. Hasegawa · H. Wakabayashi ·
K. Yoshida · A. Uchida · A. Sudo
Department of Orthopaedic Surgery, Mie University Graduate
School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: meiten@clin.medic.mie-u.ac.jp

A. Nishimura · K. Kato
Department of Orthopaedics and Sports Medicine,
Mie University Graduate School of Medicine, Tsu, Mie, Japan

T. Yamada
Department of Translational Medical Science, Mie University
Graduate School of Medicine, Tsu, Mie, Japan

physical and psychological needs of the patients. The possibility and predicted speed of KOA progression in the contralateral knee is important, as it may influence therapeutic approaches. A further reason for obtaining the estimated rates of progression is to estimate sample sizes when planning clinical trials. To the best of our knowledge, only one study [11] has estimated the rate of incidence of KOA in the contralateral knee in a population-based cohort study.

The purpose of this study was to investigate the prevalence and characteristics of unilateral KOA, to investigate what percent of the contralateral healthy knees in the unilateral KOA group progressed to KOA, and to investigate whether knee fractures influence unilateral KOA.

Materials and methods

The Miyagawa cohort study, a population-based study, began in 1997 in Miyagawa, a mountain village located in the center of Mie Prefecture, Japan. Participants were self-recruited, community-dwelling volunteers who were ≥ 65 years old. Studies were performed every two years from 1997 to 2009 at Houtoku Hospital in the village, for a total of seven studies. The population of the village was 4196 in 1997, when 1463 of the residents met the age criterion. The population dropped to 3490 in 2010, at which time 1553 individuals met the age criterion. A total of 1239 inhabitants (786 women and 453 men) participated in these studies at least once. The Committee for the Ethics of Human Research of Mie University approved the study protocol, and all participants provided their written informed consent before study enrollment. Using data from the Miyagawa cohort study, individuals who were found at a baseline screening examination to have unilateral KOA were investigated.

Baseline data obtained from standard questionnaires administered by orthopedic surgeons included information regarding age, sex, medical history, knee fracture history, and knee pain. Knee fractures were defined as including the patella, distal femur, and proximal tibia (such as the tibial plateau). Knee pain was determined from the question, "Have you experienced knee pain lasting for over one month during the past year?" Knee pain was recorded as absent, unilateral, or bilateral. Height and weight were measured, and the body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

All participants had anteroposterior (AP) radiographs of both knees in the fully extended position with the same equipment. These radiographs were scored blind to clinical details according to the Kellgren–Lawrence (K/L) grading system [13] that uses the following grades: 0,

normal; 1, possible osteophytes only; 2, definite osteophytes and possible joint space narrowing; 3, moderate osteophytes and/or definite joint space narrowing; and 4, large osteophytes, severe joint space narrowing, and/or bony sclerosis. Confirmed radiographic KOA was defined as a K/L grade of ≥ 2 . All knee radiographs were independently evaluated by three orthopedists, and the final score was reached by consensus among two or three of the orthopedists, but the median score was accepted when the opinions of all three differed. Ankylosing spondylitis was not identified in any of the participants. Knees that had undergone total knee replacements (TKA) were defined as having KOA.

The following factors were examined. Firstly, based on the first knee X-ray examination for each participant, the participants were classified into three groups: no OA (N group), unilateral KOA (U group), and bilateral KOA (B group). Moreover, the U group was classified into two subgroups: K/L grade II–I combination (II–I group), and the U group without the II–I combination ($G > 2$ group; participants in this group had one knee grade that differed by two or more grades from that of the other knee). These groups were compared in terms of physical characteristics such as age, sex, height, weight, BMI, and knee pain. Secondly, to investigate whether knee fractures influenced unilateral KOA, the percent of participants with a knee fracture history was examined in each group. Knee fractures were defined as patellar fracture, tibial plateau fracture, and/or distal femur fracture. Thirdly, the natural history of the contralateral (healthy) side knee was examined in the U group. The subjects of this series were participants in the U group who had participated in the examinations at least twice. Changes in the contralateral (healthy) side knee K/L grade U group over 2–12 years were recorded, and we determined whether the KOA had changed (K/L grade ≥ 2). Moreover, the incidence of KOA was compared between those with and without a history of knee fracture.

Statistical analysis

Mean \pm standard deviations (SD) were calculated for variables unless otherwise noted. Associations among the physical characteristics among the groups were determined by the unpaired *t* test. The relationships between KOA and knee fractures were analyzed using age, sex and BMI-adjusted logistic regression analyses with the Bonferroni correction. The change in the contralateral (healthy) side knee of the U group was analyzed by Kaplan–Meier analysis with the log-rank test. The significance level for entry into the model was 0.05. All data were analyzed using the PASW Statistics (version 18) software package (SPSS, Chicago, IL, USA).

Table 1 Characteristics of the participants with no knee osteoarthritis, bilateral knee osteoarthritis, and unilateral knee osteoarthritis

	N group (<i>n</i> = 837)	B group (<i>n</i> = 264)	U group (<i>n</i> = 122)	
			II-I group (<i>n</i> = 96)	G>2 group (<i>n</i> = 26)
Age	71.0 ± 6.6	73.5 ± 7.5*	72.4 ± 6.9	73.8 ± 5.5**
Sex (female/male)	480/357	210/54*	70/26*	15/11 ^{††}
Height (cm)	152.1 ± 8.3	149.6 ± 8.5*	149.1 ± 8.3*	151.9 ± 9.7
Weight (kg)	53.2 ± 19.2	55.6 ± 10.1**	52.9 ± 9.0 ^{††}	55.7 ± 11.8
BMI (kg/m ²)	22.9 ± 8.5	24.8 ± 3.6*	23.7 ± 3.2 ^{††}	23.9 ± 3.2
Knee pain (-/+ /++)	589/147/100	79/69/116*	39/32/25* [†]	11/9/6**

Knee pain defined as: -, absent; +, unilateral; ++, bilateral

N group no knee osteoarthritis group, *B group* bilateral knee osteoarthritis group, *U group* unilateral knee osteoarthritis group, *BMI* body mass index

p* < 0.01 versus N group, *p* < 0.05 versus N group, [†]*p* < 0.01 versus B group, ^{††}*p* < 0.05 versus B group

Table 2 Distribution of Kellgren–Lawrence grades at baseline in the unilateral knee osteoarthritis group

K/L grade	II-0	II-I	III-0	III-I	IV-0	IV-I	TKA-0	TKA-I
Participants	8	96	2	13	0	2	0	1
%	6.6	78.7	1.6	10.7	0.0	1.6	0.0	0.8

OA osteoarthritis, K/L grade Kellgren–Lawrence grade, TKA total knee arthroplasty

Results

Of the 1239 participants who attended at least one of the seven examinations associated with this study, 16 patients with rheumatoid arthritis were excluded, and a total of 1223 villagers fulfilled the study criteria.

Table 1 shows the physical characteristics of the four groups. The percentages of participants who were classified into the N, B, and U groups (II-I and G>2 groups) were 68.4, 21.6, and 10.0 % (7.8 and 2.1 %), respectively. The B group differed significantly from the N group in terms of age, sex, height, weight, BMI, and knee pain. The II-I group differed significantly from the N group in terms of sex, height, and knee pain. The G>2 group differed significantly from the N group in terms of age and knee pain. The II-I group differed significantly from the B group in terms of weight, BMI, and knee pain. There was a significant difference in sex between the G>2 and B groups.

Table 2 shows the distribution of K/L grades at baseline for the U group. Most of the U group had the II-I combination (78.7 %), followed by the III-I combination (10.7 %), and then the II-0 combination (6.6 %). Only one participant had TKA (TKA-I combination).

Figure 1 shows the relationship between knee fracture and group. There were 28, 14, 6, and 10 participants with a knee fracture history in the N, B, II-I, and G>2 groups, respectively. The percentages of knee fractures were 3.3, 5.3, 6.3, and 38.5 % in the N, B, II-I, and G>2 groups, respectively. The G>2 group experienced more knee fractures than the N, B, and II-I groups (*p* < 0.01).

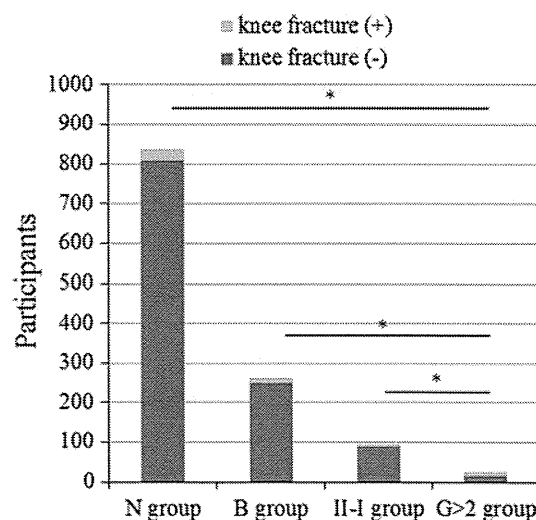


Fig. 1 Relationship between knee fracture and knee osteoarthritis. *N group* no knee osteoarthritis group, *B group* bilateral knee osteoarthritis group, *U group* unilateral knee osteoarthritis group. **p* < 0.01 versus G>2 group

Table 3 shows the natural K/L grade history of the knees in the U group over 2–12 years (average, 5.3 ± 3.2 years). A total of 65 participants in the U group participated in the examination at least twice. The percentages of participants in whom the contralateral knee had changed to KOA (K/L grade ≥ 2) were 33.3 % (1/3), 54.7 % (29/53), 0 % (0/2), 40 % (2/5), 0 % (0/1), and 0 % (0/1) in the II-0, II-I, III-0, III-I, IV-0, and TKA-I groups, respectively. Thus, 32 of 65 participants (49.2 %) proceeded to bilateral KOA. Figure 2 shows the change in the contralateral (healthy) knee in the

Table 3 Natural history of bilateral knees in the unilateral knee osteoarthritis group

Baseline K/L grade combination	Follow-up K/L grade combination										Total
	II-0	II-I	II-II	III-I	III-II	III-III	IV-0	IV-I	IV-IV	TKA-I	
II-0	1 (4.0)	1 (2.0)			1 (12.0)						3 (6.0)
II-I		21 (4.4)	17 (5.3)	3 (6.0)	4 (5.5)	7 (8.0)			1 (12.0)		53 (5.5)
III-0				1 (4.0)			1 (2.0)				2 (3.0)
III-I				2 (5.0)	1 (4.0)	1 (8.0)		1 (2.0)			5 (4.8)
IV-0											0
IV-I								1 (2.0)			1 (2.0)
TKA-0											0
TKA-I										1 (2.0)	1 (2.0)

The numbers in parentheses are the average numbers of follow-up years

K/L grade Kellgren–Lawrence grade, OA osteoarthritis, TKA total knee arthroplasty

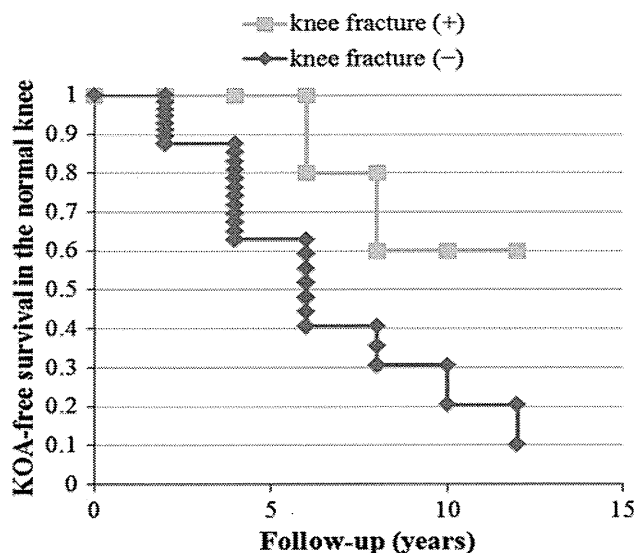


Fig. 2 The prognosis for the opposite healthy side in the unilateral knee group. The censored data in this Kaplan–Meier analysis are the normal knees (Kellgren–Lawrence grade 0 or 1). There was no significant difference between knee fracture (+) and knee fracture (–) based on the log-rank test

U group (normal knee or KOA) on Kaplan–Meier analysis and compares KOA between those with and without a history of knee fracture. There was no significant difference between those with and without a history of knee fracture based on the log-rank test.

Discussion

The present study found that the prevalences of definite radiographic bilateral and unilateral KOA were 21.6 and 10.0 % in older Japanese villagers. The present data also show that, in participants with unilateral KOA, a high percentage (49.2 %) developed OA in the contralateral healthy knee within an average of 5.3 years (range 2–12 years). A history of knee fractures had a stronger influence on the unilateral KOA group (except for those with the II-I combination) than the no KOA and bilateral KOA groups.

Davis et al. [14] reported that bilateral KOA was more than twice as prevalent as unilateral KOA in the National Health and Nutrition Examination Survey I sample. The present data showed that the B group was twice as large as the U group, so the present findings support their data. Spector et al. [11] reported that 34 % of women with unilateral KOA progressed to contralateral OA within two years. Spector et al. [14] also reported that 92 % of patients with unilateral KOA developed bilateral KOA over 11 years. The present data showed that 49.2 % participants with unilateral KOA developed bilateral KOA within an average of 5.3 years (range 2–12 years). This rate is similar to previously reported rates of 34 % for 2 years [11] and 92 % for 11 years [15]. McMahon et al. [16] reported that, in their TKA series, the percentages of bilateral KOA and unilateral KOA were 88.8 and 11.2 %, respectively. They also reported that the ten-year risk of undergoing TKA in their study population was 37.2 %, excluding

patients who underwent a contralateral TKA at the time of index surgery or within six months. Moreover, Hochberg et al. [17] reported that the presence of contralateral KOA was a risk factor for the development of definite KOA in their longitudinal study [adjusted odds ratio (OR) 6.04]. Sayre et al. [18] reported that the OR for having a contralateral knee with K/L >2 was 20.1 compared to a knee without KOA in K/L >2 knees. A contralateral knee joint grade of K/L was strongly associated with a K/L grade in the other knee. These data suggest that, with unilateral KOA, the contralateral healthy knee is at a high risk of developing KOA.

Many cross-sectional studies and a longitudinal study have reported a relationship between knee injury and KOA [14, 19–21]. Rademakers et al. [22] reported that 31 % of patients with a history of tibial plateau fractures developed secondary KOA. Marsh et al. [23] performed a review concerning the importance of anatomic reduction with respect to articular fractures. They also underlined the fact that malalignment after treatment contributes to a poor outcome after tibial plateau fractures. Experimental and observational evidence suggest that knee injuries with irregularity of the articular surface secondary to tibial plateau and distal femoral fractures, as well as angular deformity following fracture of the femoral and tibial shaft, produce increased articular surface stress, thus increasing the risk of subsequent KOA. Davis et al. [14] reported that obesity was a stronger predictor of bilateral osteoarthritis than knee injury was, with an OR of 6.6 for obesity and an OR of 3.5 for right knee injury. However, knee injury was a stronger predictor of unilateral osteoarthritis than obesity was (ORs of 3.4 and 2.4 for obesity in the right and left knee, respectively, and ORs of 16.3 and 10.9 for knee injury in the right and left knee, respectively). They concluded that different pathogenetic processes may exist for unilateral and bilateral KOA.

In the present study, the most common distribution of K/L grades at baseline for the U group was the II-I combination (78.7 %). If bilateral KOA advanced simultaneously, this combination was considered to represent the midpoint of the progression to bilateral KOA. Therefore, the relationship between the U group without the II-I combination (G>2 group) and knee fractures was examined. The G>2 group had far more cases with a knee fracture history than the N, B, and II-I groups. These data suggest that, with no history of knee fracture, the bilateral knee would become worse (and develop KOA) almost simultaneously.

The present study had several potential limitations. Firstly, Miyagawa is a mountain village, and many inhabitants are typically engaged in forestry. Secondly, participants who could attend the hospital were generally healthier than nonparticipants. Thirdly, the knee X-rays were non-

weight-bearing, so the K/L grade was underestimated. Therefore, the prevalence of KOA was lower than in other reports from Japan [2, 24]. Fourthly, other traumatic risks for KOA—knee ligament injuries [25, 26] and meniscus injuries [25–27]—were not considered in this study.

Conclusion

The prevalences of definite radiographic bilateral and unilateral KOA were 21.6 and 10.0 %, respectively, in a group of older Japanese villagers. Overall, 49.2 % of the participants with unilateral KOA developed KOA in the contralateral knee over an average of 5.3 years. A very strong association was found between unilateral KOA (except for the K/L grade II-I combination) and knee fracture. The results of the present study indicate that bilateral KOA advanced simultaneously, except in cases with a history of knee injury, such as fractures.

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

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論文

外反母趾の重症度・有病率と危険因子の検討 —第7回旧宮川村検診より—

三重大学医学系研究科運動器外科学

西村 明 展・中空 繁 登・須藤 啓 広

三重大学医学系研究科スポーツ整形外科

西村 明 展・加藤 公

要 旨 一般住民の外反母趾 (HV) の重症度, 有病率および, その危険因子を検討した報告は少ない. 今回, われわれは 1997 年より 2 年ごとにコホート研究を行っている三重県旧宮川村検診のうち, 2009 年に行われた第 7 回検診に参加した 313 名 (男 105 名, 女 208 名) を対象とし, 調査を行った. 全受診者に対して年齢, 性別, 既往歴などの問診と, 身長, 体重の測定 (BMI の算出), 両膝立位・両足立位正面単純 X 線撮影, DEXA 法による骨密度測定を行った. HV は立位単純 X 線像で HV 角 20° 以上を HV と定義し, $20^{\circ}\sim 30^{\circ}$ を軽度, $30^{\circ}\sim 40^{\circ}$ を中等度, $40^{\circ}\sim$ を重度とした. 313 例 626 足中, 軽度・中等度・重度はそれぞれ 80 足・40 足・10 足であった. 少なくとも片足が HV である住民は 81 例 (25.9%), 両足とも HV なしの住民は 232 例 (74.1%) であった. 危険因子の検討では女性が男性の 3.8 倍, どちらか一方でも膝 OA を有する群は膝 OA を有しない群に比べ 2.3 倍 HV になりやすかった.

はじめに

外反母趾の疫学研究は患者ベースでの研究が多く, 一般住民ベースの研究は比較的少ない²⁾. また, 過去の報告では単純 X 線像での計測ではなく, 足部トレースやフットプリントからの計測の報告が多い¹⁾³⁾. そこで本研究の目的は一般高齢者を対象に単純 X 線像を用いて外反母趾の重症度・有病率・危険因子につき, 横断研究を行うことである. 1997 年より 2 年毎にコホート研究を行っている三重県旧宮川村検診のうち, 2009 年に行われた第 7 回検診に参加した 65 歳以上の地域住民を対象に X 線上の重症度, 有病率と危険因子を調査した.

対象と方法

2009 年に行われた第 7 回旧宮川村検診を受診した 313 名 (男性 105 名, 女性 208 名) を対象とした. 旧宮川村 (現 三重県大台町) は林野率 96% の林業を主産業とした山村であり, 2010 年の全人口は 3490 人であるのに対し, 65 歳以上人口は 1553 人と

高齢化の進行した地区である. 全受診者に対して医師の診察を行い, 年齢, 性別, 既往歴などの問診を行った. 身長, 体重の測定と BMI の算出, 両膝立位・両足立位正面単純 X 線撮影および前腕骨 DEXA 法による骨密度測定も行った.

外反母趾は外反母趾ガイドライン⁵⁾に基づいて両足立位単純 X 線像で HV 角 20° 以上を HV と定義し, $20^{\circ}\sim 30^{\circ}$ を軽度, $30^{\circ}\sim 40^{\circ}$ を中等度, $40^{\circ}\sim$ を重度とした. 両足立位単純 X 線像は Tanaka ら⁶⁾ の報告に準じて, 管球の傾きは垂直方向に対して 15° の傾きで, 管球との距離は 100 cm とした. 有病率を重症度別に算出するとともに, HV あり群と HV なし群で, 年齢・性別・BMI・変形性膝関節症 (膝 OA) の有無 (膝 X 線像にて Kellgren & Lawrence 分類⁴⁾ で Grade 2 以上を膝 OA と定義)・骨粗鬆症の有無 (T-score $< -70\%$ を骨粗鬆症と定義)・ヘバーデン結節の有無・腰痛の有無を変数としてロジスティック回帰分析で多変量解析を行い, オッズ比 (OR) と 95% 信頼区間 (95%CI) を算出した.

Key words : hallux valgus (外反母趾), epidemiology (疫学), prevalence (有病率), severity (重症度), risk factors (危険因子)

連絡先: 西村明展 〒514-8507 三重県津市江戸橋 2-174 三重大学医学部整形外科教室

TEL 059-231-5022 FAX 059-231-5211

結 果

313例626足中、両足にHVを有するものは49例(15.7%)、片足のみにHVを有するものは32例(10.2%)であった(図1)。626足中の重症度は軽度が80足、中等度が40足、重度が10足であった(図2)。少なくとも片足がHVであるHVあり群は81例(25.9%)、HVなし群は232例(74.1%)であった。HVの危険因子の検討では性別が女性であること

(OR: 3.79, 95%CI: 1.84-7.81), BMIが低値であること(OR: 0.90, 95%CI: 0.83-0.98), 膝OAを有すること(OR: 2.26, 95%CI: 1.29-3.97)が危険因子であった(表1)。

考 察

本研究の結果では65歳以上高齢者の25.9%が少なくとも片足にHVを有していた。HVは女性が男性の3.79倍、どちらか一方でも膝OAを有する群は膝OAを有しない群に比べ2.26倍HVになりやすいという結果が得られた。

外反母趾の頻度について、Choら²⁾はHV角15°以上をHVと定義すると40~69歳までの韓国一般住民では563名中364名(64.7%)にHVが認められたと報告しており、これらのうち、HV角25°以上のものは48名(13.2%)であったと報告している。Roddyら⁶⁾はprimary care病院患者へのアンケートを行い、外反母趾を自覚しているものの頻度は40~80歳で28.4%であったと報告している。本邦では佐藤ら⁷⁾が一般中学生を対象としてHV角20°以上を外反母趾と定義すると中学1年生では男子6.7%, 女子34.8%, 中学3年生では男子15.4%, 女子22.1%がHVであったと報告している。本研究で

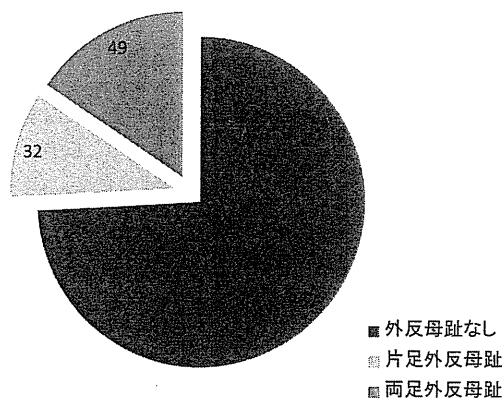


図1 外反母趾の片足・両足有病率。

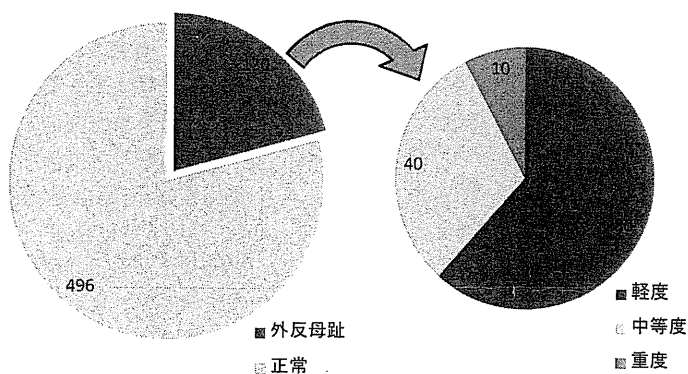


図2 外反母趾の重症度。

表1 外反母趾の危険因子

	HVあり群	HVなし群	危険率	95% CI	オッズ比
年齢	76.6±6.6	75.3±6.0	$p=0.1714$	0.986-1.081	1.032
性別	M: 13/F: 68	M: 92/F: 140	$p=0.0004$	1.778-7.851	3.671
BMI	22.8±3.9	23.6±3.2	$p=0.0106$	0.894-0.975	0.927
膝OA	+53/-28	+99/-133	$p=0.0059$	1.256-3.891	2.212
骨粗鬆症	+27/-54	+65/-167	$p=0.3108$	0.384-1.357	0.721
ヘバーデン結節	+39/-42	+86/-146	$p=0.4567$	0.710-2.142	1.233
腰痛	+37/-44	+118/-114	$p=0.4052$	0.460-1.369	0.793

は25.9%という結果であり, Choら²⁾の報告とHVの有病率に差を認めるが, HV角の基準を考慮するとはほぼよく似た頻度になるのではないかと考えられた.

外反母趾の危険因子について, Choら²⁾は女性であること, 仕事が肉体労働ではないこと, 高BMIであることをあげている. Roddyら⁶⁾は加齢, 女性, 膝関節痛, 変形性関節症, 母趾痛, 関節リウマチを危険因子にあげている. また, Barnicotら¹⁾は女性が男性に比べ, HV角が4.1度大きいと報告している. これらの報告と本研究結果を比較すると, 女性, 変形性膝関節症の存在は過去の報告とも合致するところであるが, 低BMIについてはChoら²⁾の報告と相反する結果が出た. 住民サンプルの違い, 年齢層の差, 人種差などの影響が考えられ, 今後のさらなる検討が必要と考えられた.

本研究の限界は一地区に限られた住民であるということ, 対象者数が313名と少ないこと, 検診所まで自身で来ることができる比較的健康な高齢者のみが対象であることがあげられる.

ま と め

1. 地域住民を対象として外反母趾の有病率, 重症度および危険因子の調査を行った.
2. 住民の25.9%に外反母趾を認め, 足別重症度は軽度が61.5%, 中等度が30.8%, 重度が7.7%であった.
3. 外反母趾の危険因子は女性, 低BMI, 膝OAを有することであった.

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● *Original Contribution*

EVALUATION OF THE ACCURACY OF ARTICULAR CARTILAGE THICKNESS MEASUREMENT BY B-MODE ULTRASONOGRAPHY WITH CONVENTIONAL IMAGING AND REAL-TIME SPATIAL COMPOUND ULTRASONOGRAPHY IMAGING

SATORU OHASHI, ISAO OHNISHI, TAKUYA MATSUMOTO, MASAHICO BESSHO, JUNTARO MATSUYAMA, KENJI TOBITA, MASAKO KANEKO, and KOZO NAKAMURA

Department of Sensory and Motor System Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan

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Abstract—The present study aimed to quantify the thickness of articular cartilage (Tc) *in vitro* using both conventional and real-time spatial compound B-mode ultrasonography (US) with a clinically used transducer and to evaluate the accuracy of measurement by comparing the results with values obtained microscopically. Femoral condyle samples were obtained from a 6-month-old pig and a 3-year-old pig. B-mode US images with conventional imaging and real-time spatial compound imaging (RTSCI) of osteochondral blocks were acquired. Tc determined using US (Tc-US) was measured from line data parallel to US beam direction acquired from B-mode images with an objective method for determining cartilage surface and bone-cartilage interfaces at the peak brightness values. Tc was also determined under microscopy (Tc-optical) using the corresponding points from US measurement. Tc-US was compared with Tc-optical to assess accuracy. Tc-US correlated significantly with Tc in both conventional imaging and RTSCI ($r = 0.961, 0.976$, respectively). Bland-Altman plots showed mean differences between Tc-optical and Tc-US were -0.0073 mm and 0.0139 mm with standard deviations of 0.171 mm and 0.131 mm for conventional imaging and RTSCI, respectively. Our results show that Tc-US measurement using B-mode US allows accurate measurement of Tc. Considering correlation coefficients between Tc-US and Tc-optical, RTSCI US may offer higher accuracy for measuring Tc than conventional methods when an objective tissue border determination algorithm is used, even though both showed good accuracy in our study. (E-mail: soohashi-ty@umin.ac.jp) © 2012 World Federation for Ultrasound in Medicine & Biology.

Key Words: Cartilage thickness (Tc), Ultrasonography (US), Real-time spatial compound imaging (RTSCI), Accuracy.

INTRODUCTION

Articular cartilage maintains a function of load absorption through its composition and shape. In osteoarthritis (OA) of the knee, cartilage degenerates and becomes worn due to many factors, including aging and long periods of exposure to mechanical stress. In clinical practice, conventional radiography is typically used to evaluate the status of OA. This does not show an actual image of the cartilage but instead allows evaluation of the two-dimensional (2-D) joint space width between the femoral and tibial bone surfaces, as well as the presence of osteophytes and sclerosis of subchondral bone (Kellgren and

Lawrence 1957). A key limitation of this evaluation is that cartilage thickness (Tc) on the femur cannot be differentiated from that on the tibia or from the meniscus. Since the regions of femoral and tibial cartilage included in evaluations of 2-D joint space width are affected by the degree of knee flexion and the intra-articular distribution of cartilage loss in OA is heterogeneous, the technical validity of joint space width measurement depends on the repeatability of the position of the femur relative to the tibia (Peterfy and Kothari 2006), which could be difficult to achieve on serial examinations.

Based on these limitations of conventional radiography, direct evaluation of cartilage has been studied using magnetic resonance imaging (MRI). This modality allows morphologic evaluation of articular cartilage, such as determination of thickness and volume (Eckstein et al. 2008) and identification of cartilage degeneration

Address correspondence to: Satoru Ohashi, M.D., Ph.D., Department of Sensory and Motor System Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: soohashi-ty@umin.ac.jp

(Multanen *et al.* 2009). Tc has been quantified by creating a three-dimensional (3-D) cartilage model from MRI slice scans (Eckstein *et al.* 2006, 2007). The limitations of evaluation using MRI, however, are that the image acquisition time is relatively long (which could lead to body movement and patient discomfort), the cost of imaging is relatively high and MRI sometimes cannot be performed on patients with specific implants in their bodies (*e.g.*, pacemakers). For these reasons, development of methods for measuring Tc using other imaging modalities as a screening test or for relatively inexpensive, quick and noninvasive follow-up of OA could be useful. We think that ultrasonography (US) could represent the most appropriate imaging modality. In fact, musculoskeletal US has been gaining popularity, since this technique allows high-resolution, real-time imaging of articular and periarticular structures and has the advantages of being nonradioactive, inexpensive, portable, highly acceptable to patients and repeatable (Kane *et al.* 2004). A qualitative evaluation study has shown that US findings such as effusion and protrusion of the medial meniscus are associated with clinical assessments in OA (Naredo *et al.* 2005).

The availability of US for the examination of articular cartilage has been investigated, as this technique allows direct visualization of the articular cartilage. Degenerative changes of cartilage have been evaluated by US (Kaleva *et al.* 2008; Wang *et al.* 2010), along with cartilage surface roughness (Chiang *et al.* 1994; Wang *et al.* 2010). A-mode signals, as radio-frequency wave signals of US, have previously been used for the measurement of Tc (Adam *et al.* 1998; Cherin *et al.* 1998; Jurvelin *et al.* 1995). The accuracy of ultrasonographic measurement of Tc has been evaluated in comparison with optical measurement, with ultrasonographic thickness and optical thickness showing good agreement (Jurvelin *et al.* 1995).

B-mode imaging on US creates a 2-D image based on the brightness value in each pixel converted from the radio-frequency signal intensity and has been used to visualize articular cartilage and evaluate Tc in both an *in vitro* experimental study using osteochondral blocks of human knees (Myers *et al.* 1995) and clinical studies (Aisen *et al.* 1984; Castriota-Scanderbeg *et al.* 1996; McCune *et al.* 1990; Moller *et al.* 2009). These studies have shown good agreement of Tc measured on US with histologic measurement values (Myers *et al.* 1995) and histologic findings (Aisen *et al.* 1984; McCune *et al.* 1990), along with high precision for Tc measurement using US (Castriota-Scanderbeg *et al.* 1996; Moller *et al.* 2009). However, accuracy assessment of Tc measurement has only been performed *in vitro* (Myers *et al.* 1995) using a relatively high frequency (25 MHz) over a relatively narrow area of articular cartilage and accuracy assessment of Tc measurement using B-mode US using a clinical US

linear transducer has not previously been studied. With a clinical US linear transducer, however, tissue borders such as bone-cartilage interfaces are visualized as a high-intensity band in B-mode image and determination of the border could be subjective. In addition, an obstacle to evaluating the accuracy of Tc measurement using the clinical linear transducer is the technical difficulty of identifying the US scan plane and guaranteeing registration between the US scan plane and the histologic or optical evaluation plane. Nevertheless, we believe it is important to evaluate the accuracy of Tc measurement in B-mode imaging.

Clinical use of B-mode US, on the other hand, shows several obstacles to the acquisition of clear images of articular cartilage. One of these is acoustic artifacts, such as speckle or clutter, which are characteristic of US. Such artifacts usually do not deteriorate the US images to a large extent and are acceptable from the perspective of qualitative evaluation. However, we assumed these artifacts would affect measurement values in quantitative evaluation of tissues and reduction of artifacts could, thus, prove beneficial for quantitative evaluation using clinical B-mode US. One of the methods for reducing these factors is real-time spatial compound imaging (RTSCI) (Entrekin *et al.* 2001), a technique that uses electronic beam steering of a transducer array to acquire several overlapping scans of an object from different view angles. These scans are then combined to produce a single image (Carpenter *et al.* 1980; Entrekin *et al.* 2001; Jespersen *et al.* 1998; Lin *et al.* 2002; Shattuck and von Ramm 1982). RTSCI has been used in studies on blood vessels (Jespersen *et al.* 2000; Kofoed *et al.* 2001; Yen *et al.* 2009), breast (Cha *et al.* 2005; Huber *et al.* 2002), thyroid (Shapiro *et al.* 2001), liver (Yen *et al.* 2008), abdomen and pelvis (Oktar *et al.* 2003) and skin (Wortsman *et al.* 2004), as well as musculoskeletal tissues, such as meniscus (Shanbhogue *et al.* 2009), Achilles tendon (Bartolotta *et al.* 2007) or knee ligament (Sorrentino *et al.* 2009). Musculoskeletal tissues, such as tendons or ligaments, are specular or mirror-like reflectors, with which the echo amplitude from the tissue is highly dependent on the angle of incidence of the US beam, with the strongest occurring when the US beam is perpendicular to the reflector (Entrekin *et al.* 2001). RTSCI has been suggested to be effective on musculoskeletal tissues, since scanning the joint from multiple angles with RTSCI allows curved interfaces to be shown as more continuous (Entrekin *et al.* 2001).

Shanbhogue *et al.* reported detection of marginal meniscus tears using RTSCI with sensitivity, specificity and accuracy of 90% each and without interobserver variability, whereas conventional US showed sensitivity, specificity and accuracy within the range of 80%–88%

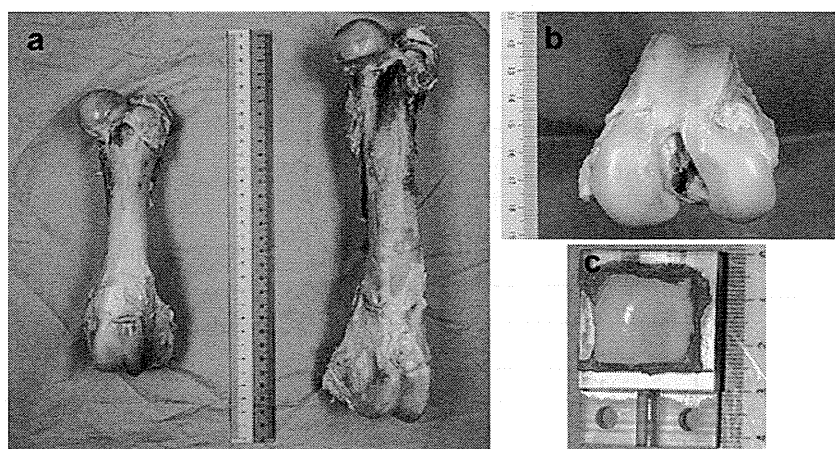


Fig. 1. (a) Porcine femora from a 6-month-old pig (left) and a 3-year-old pig (right). (b) Cartilage surface of the femoral condyle. (c) An osteochondral block fixed to a sample holder.

and the presence of interobserver variability (Shanbhogue et al. 2009). Bartolotta et al. reported that 72 of 80 examinations using RTSCI exhibited better performance with respect to sonographic artifacts than conventional US in diagnosing Achilles tendon xanthomas in patients with heterozygous familial hypercholesterolemia (Bartolotta et al. 2007). RTSCI, however, has never been applied to the evaluation of articular cartilage. We assumed that RTSCI would prove effective in evaluating articular cartilage.

The purposes of this study were to quantify articular Tc *in vitro* with an objective method for determining cartilage surface and bone-cartilage interfaces using both conventional and real-time spatial compound B-mode ultrasonography with a clinically used transducer and to evaluate the accuracy of measurement by comparing the results with measurement values obtained optically.

METHODS

Cartilage sample preparation

The animal care and use committee at our university approved all procedures used in this investigation. Knee joints of a 6-month-old pig and a 3-year-old pig were obtained from a slaughterhouse (Tokyo Shibaura Zouki, Tokyo, Japan), as we assumed that Tc might differ between pigs at different ages (Fig. 1). Porcine femoral condyle articular cartilage was used in this study, since the cartilage size and shape are relatively similar to human cartilage. After slaughter, whole bodies of pigs were kept at 3°C in a refrigerated room. On the third day, the hind limbs were detached and sent to our facility at the same temperature. In our facility, limbs with intact knee joints were packed in plastic bags, degassed, sealed hermetically, and stored at -20°C. On the day of the experiment, soft tissues including the joint capsules and ligaments were removed after the limbs were thawed in

normal saline solution (Otsuka Pharmaceutical, Tokyo, Japan) at room temperature. Osteochondral blocks from the left medial femoral condyles were acquired by cutting the bone with a band saw (SWD-250; Fujiwara Sangyo, Miki, Japan) and then fixing the sample on a custom-made acrylic sample holder (30 × 30 × 13 mm; Murai and Co., Tokyo, Japan) with resin (GC-Ostron; GC, Tokyo, Japan) (Fig. 1). During preparation, samples were continuously cooled and moistened using normal saline solution.

Image acquisition and Tc measurement by US

Acoustic measurements were performed in the following manner. The sample holder with the porcine osteochondral block affixed was positioned in the center of an acrylic frame, which was filled with normal saline solution at room temperature (Fig. 2). Three nylon strings were set in the frame in a figure of eight, so that the intersection of each string lay halfway between the sidewalls of the frame. Two intersections were aligned vertically (points a and b in Fig. 2) and two intersections were aligned horizontally (points a and c). The strings were set so that a perpendicular bisector of a line segment of the pair of the two horizontal intersections ran through the center of the sample holder.

A B-mode 10.0-MHz linear ultrasound transducer (UST-5411; Aloka, Tokyo, Japan) connected to an ultrasound device (Prosound ALPHA 10; Aloka) was attached to a multijoint holding arm, which was fixed to a stage (Fig. 3). The multijoint holding arm was fixed at the position where the B-mode image contained the three intersection points of nylon strings, so that the B-mode US beam plane shared the same plane as the center cross-section plane of the acrylic sample holder. In addition, since the two intersection points of nylon strings were horizontal (points a and c in Fig. 2) and the multijoint holding

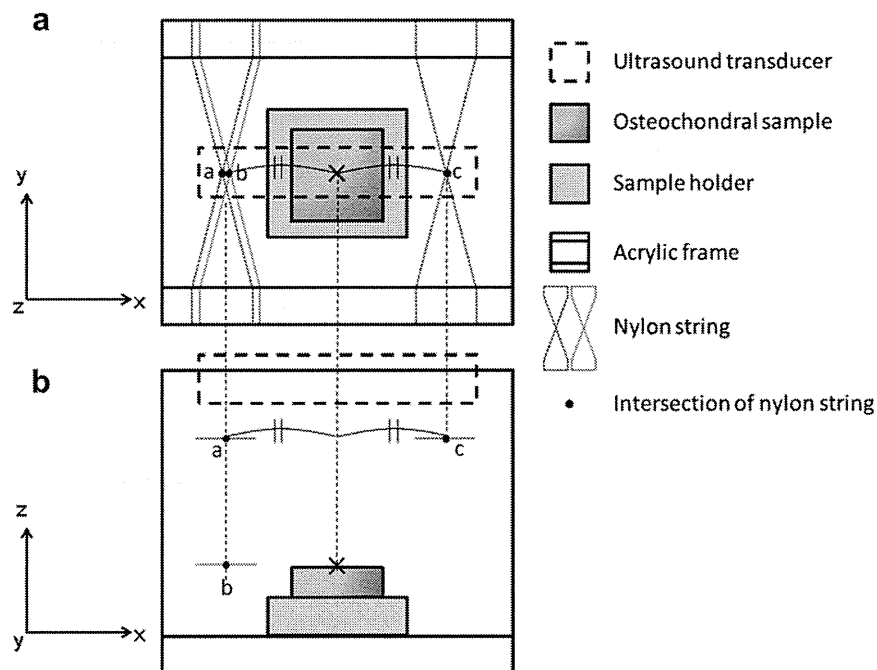


Fig. 2. Schematic showing the custom-made apparatus for US image acquisition, viewed from the top (a) and from the side (b). The sample holder in the center of an acrylic frame and three nylon strings were set in the frame in a figure of eight. Two intersections (points a and b) were aligned vertically and two intersections (points a and c) were aligned horizontally. The strings were set so that a perpendicular bisector of a line segment connecting points a and c would run through the center of the sample holder.

arm was fixed at the position where those intersection points were horizontal in the B-mode image, the direction of the conventional B-mode US beam and the neutral B-mode US beam of the spatial compound imaging were vertical. The distance between the cartilage surface and the transducer surface was set at the transducer focus distance (ca. 20 mm in the z-axis direction of the sample holder coordinate). B-mode images of the center cross-section plane of the sample holder were acquired. Image settings were for both conventional imaging (tissue harmonic imaging) and RTSCI superimposed with three frames, each from different viewing angles of -20° , 0° , and 20° to the right angle. System settings were opti-

mized to image the cartilage surface ($420 \text{ pixels} \times 468 \text{ pixels}$; pixel size, $0.0855 \text{ mm} \times 0.0855 \text{ mm}$).

B-mode image data with brightness information for each pixel with 256 shades of gray were imported to originally developed software (Fig. 4) and slice images were aligned so that two line segments that connected the three intersection points of the nylon strings in the US images became horizontal and vertical, respectively, to match the direction of the x-z axis of the sample coordinate and the US image. Following this fine adjustment of image alignment, the line brightness data of the perpendicular bisector of the line segment connecting the horizontal intersection points (points a and c in Fig. 2), which

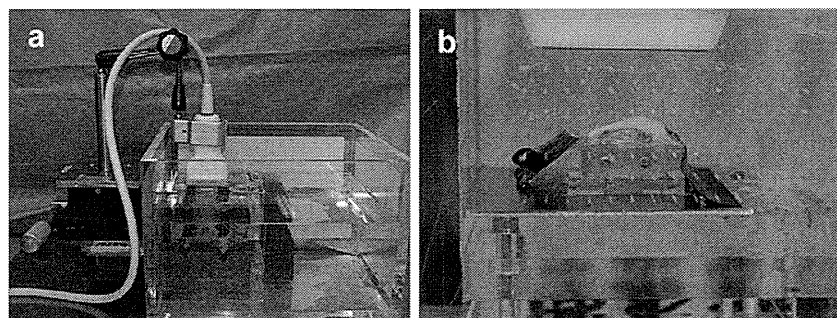


Fig. 3. (a) A B-mode 10.0-MHz linear ultrasound transducer was attached to a multijoint holding arm, which was fixed to a stage equipped with two micrometers for position adjustment by parallel movement (x and y axes). (b) The multijoint holding arm was fixed at the position where the B-mode image contains the three intersection points of nylon strings (points a, b and c in Fig. 2).

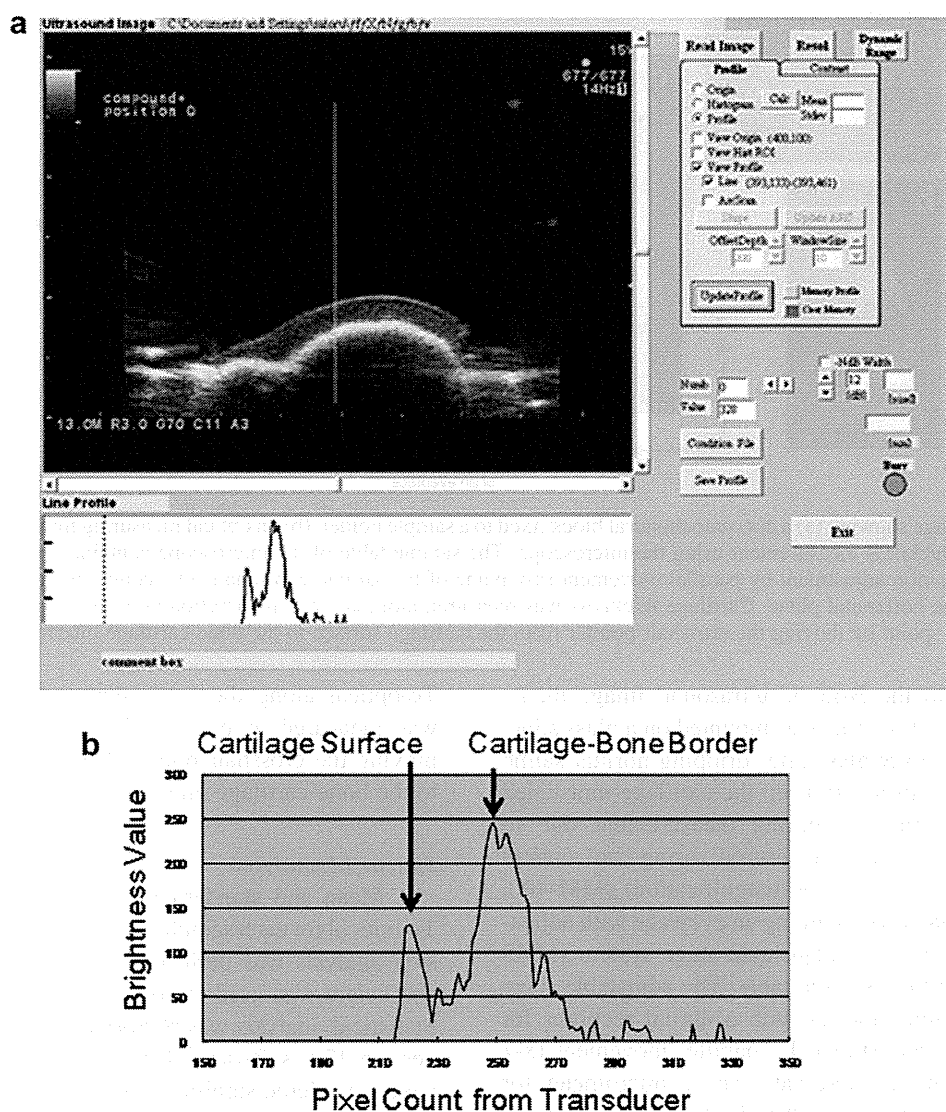


Fig. 4. (a) B-mode image data were imported into the originally developed software and line brightness data of the center line of the sample holder parallel to the z-axis, as well as line brightness data for 30 points at 0.5-mm intervals parallel to US beam direction (z-axis direction of the sample coordinate), were acquired. (b) The cartilage surface and bone-cartilage interface of the specimen were defined as the brightness peaks of each reflected signal. Cartilage thickness (Tc-US) was measured as the distance between the peaks.

corresponds to the center line of the sample holder parallel to the z-axis, were acquired. In addition, line brightness data parallel to the US beam direction (z-axis direction) for 30 points (15 points on the each side from the center line) at 0.5-mm intervals (15 mm wide in x-axis direction) in each B-mode image were obtained from both the 6-month- and 3-year-old pigs. The cartilage surface and cartilage-bone border of the specimen were defined as the brightness peaks of each reflected signal (Fig. 4). Cartilage thickness (Tc-US) was measured as the distance between peaks, which was adjusted by the ultrasound speed for each age from our past study (Ohashi et al. 2011) (1488 m/s and 1709 m/s for a 6-month- and a 3-year-old pig, respec-

tively) and the reference speed of the ultrasound system (1530 m/s).

Microscopic thickness measurement

For the measurement of Tc, direct optical measurement using microscopy of the cross-section of the sample was performed (Tc-optical). The sample holder with the osteochondral sample was attached to the holding arm of a diamond saw device (Minitom; Struers, Ballerup, Denmark), such that the saw blade was vertical to the top surface of the sample holder and parallel to the x-axis of the sample holder coordinate. By adjusting the position of the arm within an accuracy of 10 μ m, a center-cut plane of the acryl sample holder was created,