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## Disclosures:

This study was conducted by the Task Force of the Committee of Physical Therapy of the Japanese Orthopaedic Association.

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## ORIGINAL RESEARCH ARTICLE

# Effect of Home Exercise of Quadriceps on Knee Osteoarthritis Compared with Nonsteroidal Antiinflammatory Drugs

## A Randomized Controlled Trial

### ABSTRACT

Doi T, Akai M, Fujino K, Iwaya T, Kurosawa H, Hayashi K, Marui E: Effect of home exercise of quadriceps on knee osteoarthritis compared with nonsteroidal antiinflammatory drugs: a randomized controlled trial. *Am J Phys Med Rehabil* 2008;87:258–269.

**Objectives:** To examine the effect of home-based exercise on knee osteoarthritis among Japanese in comparison with that of nonsteroidal antiinflammatory drugs (NSAIDs).

**Design:** An open-labeled, randomized, controlled, multiclinic trial compared home-based quadriceps exercise with NSAIDs. Treatments were basically evaluated after 8 wks and compared with the baseline scores. Outcomes were evaluated with a set of psychometric measurements including the Western Ontario and McMaster Universities Arthritis Index (WOMAC), 36-Item Short-Form Health Survey (SF-36), Japanese Knee Osteoarthritis Measure (JKOM), and pain with the visual analog scale.

**Results:** A total of 142 patients entered this trial to provide the baseline data. After 21 cases withdrew, the final number analyzed was 121 cases: 63 for the exercise group and 58 for the NSAIDs group. Between these two groups, there was no significant difference in gender, age, body height and weight, body mass index, or each score at baseline. The subjects in both groups showed improvements in all scores at the end of intervention. The difference in improvement rate of each score between the two groups was not statistically significant, though the mean rank score measured with JKOM in the exercise was slightly better than that of the NSAIDs.

**Conclusions:** Home-based exercise using quadriceps strengthening improves knee osteoarthritis no less than NSAIDs.

**Key Words:** Knee Extension, Isotonic Exercise, Psychometric, Resistance Exercise, Pain, Function

Osteoarthritis is a common and major disease that brings pain and disability to elderly people. This is because so many persons complain of knee pain as a result of unavoidable degenerative aging changes and because developed countries like Japan face a drastic increase in the aged population. If we apply radiographic criteria for diagnosis to a few joints of people aged older than 60 yrs, the findings are always indicative of osteoarthritis. However, it is reported that only 10–20% of such people have significant clinical symptoms of the disease.<sup>1</sup> The outcome of surgical treatment, including total knee replacement or high tibial osteotomy, is reportedly good,<sup>2,3</sup> but such surgery is mainly limited to severe or advanced cases. As a matter of fact, the majority of patients are engaged in conservative treatment.<sup>4</sup> There is, therefore, a need to establish an effective scheme of nonoperative treatment for mild or moderate cases.

Recently, the use of outcome measures has become popular in clinical medicine. The key to solving problems in medical practice depends on valid and reliable methods to evaluate the outcomes of intervention. Outcome scales should also include patient-based outcome and health-related quality of life. When we apply a global standard of medical outcome assessment for a certain clinical problem, it is often necessary to fine-tune the standard to meet the specific condition of each country. Consequently, we developed a measure for patient-based, health-related quality of life that reflects Japanese social and cultural backgrounds. The measure is known as the Japanese Knee Osteoarthritis Measure (JKOM),<sup>5</sup> and it was used to evaluate our intervention in this study.

This was multiclinic trial performed at registered private clinics and hospitals that were members of the Japanese Orthopaedic Association and were distributed all over Japan. During the working process, to create a trial protocol and to collect other necessary data, we performed a study search and referred to related articles. Several systematic reviews<sup>6–8</sup> and clinical guideline<sup>9</sup> on exercise for knee osteoarthritis were identified at the time of making the study protocol (2002). Since 2002, there have been other reviews on exercise and osteoarthritis.<sup>10–13</sup> Collected articles gave information regarding patients being treated with considerable variations of therapeutic exercise and even exercise combined with other interventions such as drugs, diet control, lifestyle advice, or others.

Because we intended to certify directly whether home-based therapeutic exercise was effective, we selected a simple design that would compare exercise with nonsteroidal antiinflammatory drugs (NSAID) to test clinical equivalence. NSAIDs are already proven

effective for knee osteoarthritis, at least in short-term outcomes.<sup>4,14</sup>

We conducted this study to examine the effect of home exercise for knee osteoarthritis among Japanese compared with NSAIDs. In this trial, we first intended to determine the efficacy of therapeutic exercise, but we also intended to investigate treatment compliance checked by daily note recording.

## MATERIALS AND METHODS

### Design

Our primary purpose of this trial was to investigate the effect of therapeutic exercise. However, we also wanted to examine the issue of compliance with treatment as a foundation of home exercise reflected by the relationship between the patient and doctors and other staff members. To improve the patients' compliance with exercise or drug therapy, we asked the doctors to select the frequency of clinic visits (weekly *vs.* biweekly) and required the patients to keep daily records of each treatment performed. When attending physicians were registered with the study, they were asked to choose the type of hospital visit for their participating patients.

Assessment of the outcomes was done at the knee joint in unilateral cases and at the more symptomatic joint in bilateral cases.

### Administration Office

We organized a trial administration office in the department of public health, Juntendo Medical School (Prof. Eiji Marui). This administration office and an affiliated committee were authorized to keep watch on the present trial and to stop it as occasion arose. Harmful or undesired events during the trial were to be reported to the office. Various questions from the doctors who joined the trial were answered through the office.

### Ethical Review

The local institutional review board of these registered hospitals approved the protocol of the present trial. For private clinics that do not have their own review board, the National Rehabilitation Center inspected the standard operation protocol by its review committee on behalf of these clinics. As a preregistration system for clinical trials run by the University Hospital Medical Information Network (UMIN) started in Japan since July 2005, this trial was registered under approval by the Japanese Orthopedic Association and other related societies (<http://center.umin.ac.jp/cgi-open-bin/ctr/C000000268>).

### Patients

Patients were recruited from outpatient clinic groups attended by physicians who were members

of the Japanese Orthopaedic Association. Patient selection was conducted consecutively from July 2003 to April 2004. All eligible patients provided written informed consent, which was included and approved in the protocol.

### Entry Criteria

According to the report from the subcommittee on classification criteria of osteoarthritis of the American Rheumatism Association,<sup>15</sup> diagnostic entry criteria in this study for “knee osteoarthritis” were defined as (1) knee pain, (2) age over 50 yrs old, and (3) osteophytes confirmed by x-rays.

### Exclusion Criteria

Exclusion criteria in this study were as follows:

- (1) Patients who had treatment for their knee at another hospital or clinic—that is, who received therapeutic exercise, intraarticular injection, or NSAIDs within 4 wks before the day of agreement to enter the trial
- (2) Patients who had undergone or planned to have surgery on the knee within 6 mos before or after the day of agreement to enter the trial
- (3) Patients who required intraarticular injection
- (4) Patients who required aspiration of joint fluid
- (5) Patients who took bisphosphonate, vitamin K, or hormone therapy
- (6) Patients who had diseases requiring regular or intermittent use of steroid or NSAIDs
- (7) Patients who had articular cartilage injury or a history of damage attributable to obvious trauma or septic arthritis
- (8) Patients who were diagnosed as having rheumatoid arthritis, gout, pseudogout, or collagen diseases
- (9) Patients who had difficulty complying with their treatment schedule
- (10) Patients who had a history of cerebral vascular accident within 6 mos before the day of agreement to enter the trial
- (11) Patients who had a history of myocardial infarction within 6 mos before the day of agreement to enter the trial
- (12) Patients who received treatment for cardiac failure
- (13) Patients with liver dysfunction (AST, ALT more than 100 IU/liter)
- (14) Patients with renal dysfunction (serum creatinine more than 3.0 mg/dl)

For criteria 12–14, past history and laboratory data from other medical facilities were used for reference.

Patients who accepted and fitted the above criteria were invited to participate in this study and were given a questionnaire booklet and a consent form. All patients were then asked to fill in the JKOM, the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the 36-Item Short-Form Health Survey (SF-36) questionnaires, and a pain-assessment procedure using the visual analog scale (VAS) at the time of trial entry. Their attending doctors filled out their patient information sheets to check the diagnostic entry criteria, and they kept the consent forms. The sheet completed by the attending doctors was sent via facsimile to the administration office. After rechecking the information sheet, patients were randomized to either the exercise group or drug group, using a computer-generated random allocation program. The booklets were collected and sent back to the analysis team after filling out all three questionnaires.

### Laboratory and Radiologic Check

Laboratory tests including blood cell count, biochemical examination, and routine urinalysis were performed to rule out other rheumatologic or joint diseases. These blood tests and urinalysis were checked twice at the time of entry and on completion of treatment 2 mos later.

X-rays of the anteroposterior and lateral views of both knee joints in a standing position on one leg were taken following the predetermined instruction sheet; these were used to confirm the diagnosis. After the findings had been explained to the patients by attending doctors, the x-rays, which were sent to the National Rehabilitation Center within a few weeks, were assessed by the independent team of orthopedic doctors according to the Kellgren–Lawrence grading system.<sup>16</sup> Three doctors graded the x-rays independently, and in cases of disagreement the rating was determined by majority rule.

### Interventions

#### Exercise

The subjects were instructed to exercise the quadriceps muscle group by performing knee extension movements while sitting on a chair or, if necessary, in a supine position. The knee extensions were performed at a cadence of one repetition every 3–5 secs. Patients were instructed to keep the foot of the exercising leg about 10 cm above the floor during the recovery phase of each repetition. Patients performed four sets of 20 repetitions of the above quadriceps exercise every day, with two sets performed in the morning and two in the afternoon.

When patients started their exercise, they were given instructions by the doctors or therapists. Patients were supplied with an exercise instruction

sheet that was easy to follow and a notebook to record the individual exercise performed. Patients desiring heavier weight during the exercise protocol were permitted to increase the load on the ankle by 0.5-kg increments in the form of sandbags (however, almost all the patients did their exercise with their own weight).

## Drugs

NSAIDs were limited to only one of three prescribed. These are the top three used in Japan at the present: loxoprofen sodium (60-mg tablet), diclofenac sodium (25-mg tablet), and zaltoprofen (80-mg tablet). The dosages were three tablets for each drug, to be taken three times per day, which is a usual dosage for Japanese.

These NSAIDs were used with a rebamipide 100-mg tablet, sodium azulenesulfonate 0.5-g granules, or teprenone 50-mg capsule for preventing gastrointestinal adverse reactions. The patients were able to stop their drugs when they no longer required treatment. They were also required to record in a notebook exactly how they had been taking the medicine.

## Additional Treatments

In addition to treatment described in the protocol, it was permitted to use sticky plaster with analgesics. The four most common types of sticky plaster in Japan were used. These were flurbiprofen, indometacin, ketoprofen, and felbinac. They were used twice a day by patients. The sticky plaster used was also recorded in the notebooks.

## Regular Consultation

Because the compliance of patients could depend on the patient–doctor relationship, especially in home-based exercise, the frequency of clinical visits and regular consultations were checked. These were not the direct target characteristics for patients' allocation, but they were confirmed according to the selection at the entry sheet and the recording notebook for daily treatment.

## Patients' Allocation

The clinics and hospitals that wished to join the trial were registered in advance at the administration office. As a general rule, a majority of the hospitals selected outpatient clinic visits every 2 wks, and small clinics selected weekly consultation. However, there were some that which had both types of clinical visits for patients.

Subject randomization was performed at the administration office of Juntendo Medical School, using a computer-generated random table. Each participating clinic and hospital faxed patients' entry sheets to the above office where the randomization was per-

formed. The information about group allocation was then faxed back to the home institution.

## Scales

Three self-completion questionnaires—the JKOM, the WOMAC, and the SF-36—were answered by the patients in this study.

The JKOM is a self-administered, disease-specific measure. It consists of 25 items that include patient pain in level walking, standing or climbing stairs, physical functions related to the activities of daily living, and social functions including participation.<sup>17</sup> Twenty-three questions were constructed to identify disability and impairment. The content of each question was determined through repeated discussions among the committee members. The selected items reflected the contemporary lifestyles of Japanese people. This was originally written in Japanese and then was translated into English. We performed a clinical trial to investigate the psychometric properties of this measure in terms of validity and reliability.<sup>5</sup>

The WOMAC is a self-administered, disease-specific health measure, which was developed by Bellamy and others.<sup>18</sup> The WOMAC is a 24-item questionnaire grouped into the following three categories: pain, stiffness, and physical function. It was originally designed for use in clinical trials of patients with osteoarthritis of the hip and knee. The translated Japanese version was available via the Internet (<http://www.womac.org/womac>) after obtaining permission from the original author.

The SF-36 is a self-administered, generic questionnaire, which consists of 36 questions divided into eight domains.<sup>19</sup> The SF-36 was translated into Japanese and tested by Fukuhara et al.<sup>20</sup> for validity and reliability.

## Assessment Schedule

Answers to the four scores, which consisted of JKOM, WOMAC, SF-36, and VAS, were collected at the baseline (0 wk) and at the end of the 2-mo (8-wk) intervention. After the first month of treatment (4 wks), patients were asked to complete only the JKOM and VAS measures. In addition, patients who were willing completed all four questionnaires 1 mo after treatment (12 wks). The results of the scores were kept secret from the patients until the completion of each trial.

## Statistical Analysis

Among the patients' demographic data, gender ratio was analyzed with  $\chi^2$  test, and age, height, weight, and body mass index were analyzed with Student's *t* test.

The primary outcomes used to assess the effectiveness of exercise compared with NSAIDs were scores from the JKOM, WOMAC, SF-36, and VAS.

The secondary outcomes were behavioral modulation of patients, as reflected by daily notes.

Pain assessment with VAS was also performed. Patients were asked about the degree of knee pain they had experienced during the last few days. The replies were marked on a straight 10-cm line to indicate where they thought their level of pain was situated. This ranged from “no pain at all” on the far left side to “the most severe pain I’ve ever felt” on the far right.

The results of JKOM, WOMAC, SF-36, and VAS score, measurements with ordinal scale (ranking scale) at the baseline between the exercise and the NSAIDs groups, were analyzed by Mann–Whitney *U* test.

The comparison between the baseline and 8 wks in each group was tested with the Wilcoxon signed ranks test. Statistical significance was determined as less than 0.05 as shown in two-tailed asymptotic significance. In JKOM and WOMAC, improved scores are scaled in decreasing order, whereas the SF-36 scale is in increasing order. Therefore, to standardize the grading scales of the different questionnaires, a Mann–Whitney *U* test was used. The resulting values of the baseline and posttreatment scores were compared with this standardized scale in which larger values indicated an improvement in a patient’s condition. The 95% confidence interval for the difference between medians was estimated according to the method and attached software described in a statistical textbook.<sup>21</sup>

Collected patients’ data were additionally stratified in weekly and biweekly consultation groups. Distribution of weekly and biweekly clinic visits was checked with a  $\chi^2$  test.

All the statistic analyses were performed using the statistical software SPSS (version 10.0J, SPSS Inc. Chicago, IL).

### Estimated Number of Patients Needed

The number of patients recruited was based on the number needed to detect a difference of 20, 30, and 40% between the exercise and NSAIDs group on the WOMAC scale, according to a power of 0.80 and a *P* value of 0.05.

## RESULTS

### Patient Characteristics and Dropout Cases

Up to 41 registered hospitals throughout Japan and their attending doctors participated in this study. This trial had to be completed within the time schedule approved by each institutional review board and ethical committee. Participants also had to be registered from July 2003 to January 2004.

A total of 175 patients were counted by the administration office; 33 patients did not fill eligi-

bility requirements, refused to participate, or declined for other reasons. As a result, 142 patients ultimately entered this clinical trial and formed the groups providing the baseline data (Fig. 1). The flow of enrollment, allocation, follow-up, and analysis was shown according to the guideline of the CONSORT statement.<sup>22</sup>

These patients were under the care of doctors from 35 hospitals and clinics. There were no statistically significant differences between the exercise group and NSAIDs group according to  $\chi^2$  test and Student’s *t* test (Table 1). The number cases where data were incomplete or excluded from further analysis were 21 (14.8%): 9 (12.5%) in the exercise group and 12 (17.1%) in the NSAIDs group. The scores of withdrawal cases (JKOM, WOMAC, SF-36, and VAS) had no statistically significant difference between the exercise group and NSAIDs group according to a Mann–Whitney test. (The table is abridged.)

A total of 121 patients completed the present trial (63 in the exercise group and 58 in the NSAIDs group). There were no statistical differences between the exercise group and NSAIDs group in terms of gender, age, body height, weight, and body mass index (Table 1).

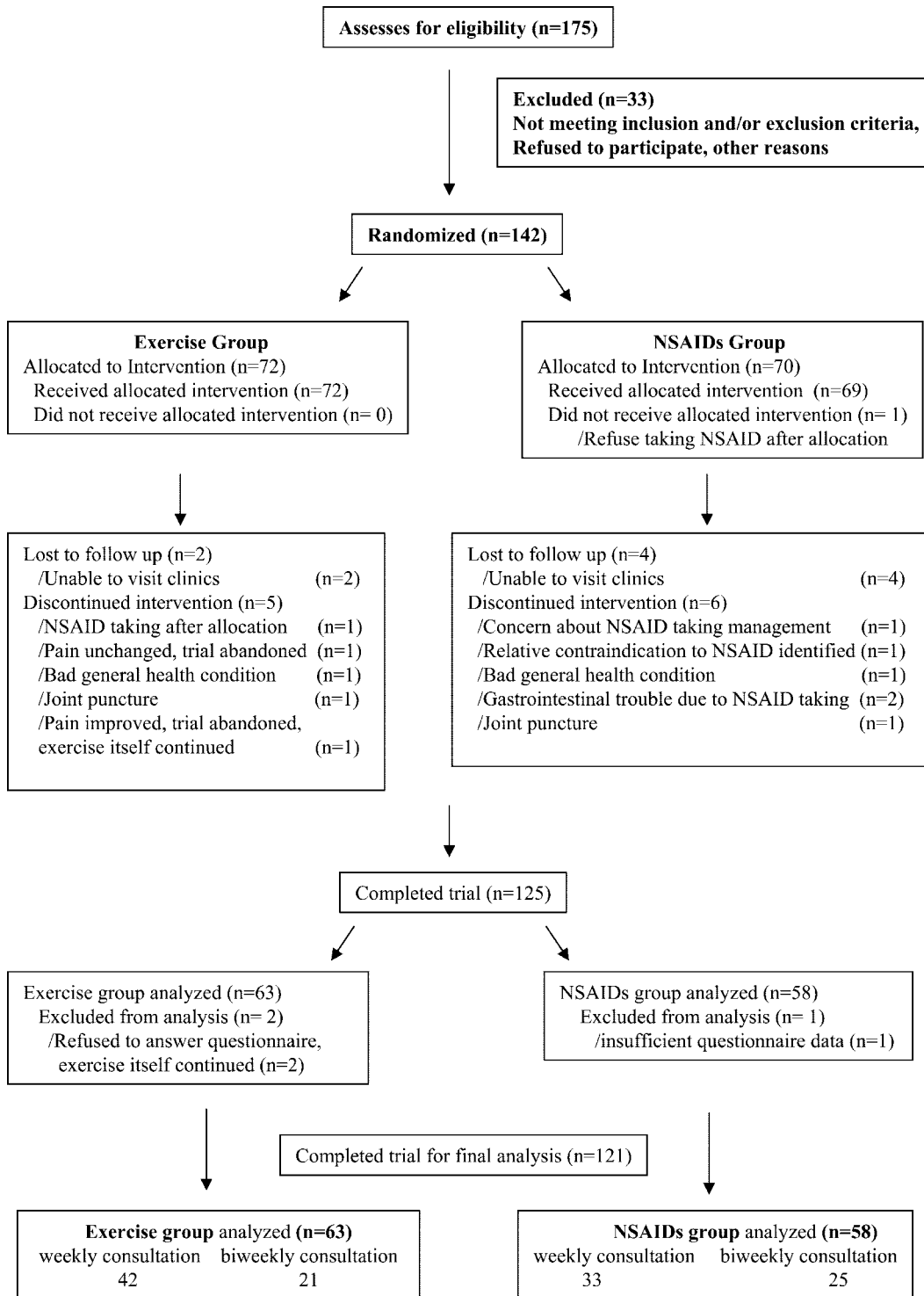
As for assessment of x-rays at baseline and at completion of the study, there were no statistical differences of grade distribution based on  $\chi^2$  test between the exercise group and NSAIDs group, according to the criteria of Kellgren and Lawrence. The majority of the cases were grade 2 or 3, but the mean rank of the exercise group showed a slightly higher (but insignificant) value based on a Mann–Whitney test compared with the NSAIDs group (*P* = 0.083 at entry and *P* = 0.094 at completion).

### Primary and Secondary Outcomes

We are not fully able to describe in the current article all of the analysis results, including patients’ compliance of treatment by assessment of the daily notebook; the influence of consultation frequency on compliance and improvements in health; and data obtained from the posttreatment (12-wk) questionnaires. Here, we report as “part I” the main results of the trial, including the comparison between home-based quadriceps exercise and NSAIDs in mild to moderate knee osteoarthritis during 8 wks of treatment. We will present the remaining results in the future as “part II.”

In the completed 121 cases, there were no statistical significant differences in each JKOM, WOMAC, SF-36, and VAS score at baseline between the exercise and the NSAIDs groups according to Mann–Whitney *U* test (Table 2).

According to a  $\chi^2$  test for the frequency of clinical visits, there was no significant difference



**FIGURE 1** Flow diagram of patients participating in this trial.

between weekly consultation (exercise group 42: NSAIDs group 33) and biweekly consultation (exercise group 21: NSAIDs group 25).

In the exercise group, all the scores for JKOM, WOMAC, SF-36, and VAS showed improvements between the baseline and the end of intervention (8 wks later) at  $P < 0.001$ . In contrast, in the NSAIDs group, the scores for JKOM,

WOMAC, and VAS improved at  $P < 0.001$ , whereas the SF-36 score improvement was slightly lower at  $P < 0.03$  (Table 2). The difference of the improvement rate (the change during the baseline and 8 wks compared with the baseline) of each score between the two groups was not significant, even though the average rank in the exercise group was slightly better than that

**TABLE 1** Comparison of two groups at the time of entry registration ( $n = 142$  cases) and at the time of trial completion ( $n = 121$  cases)

	Entry Registration ( $n = 142$ )		<i>P</i>	Trial Completion ( $n = 121$ )		<i>P</i>
	Exercise Group ( $n = 72$ )	NSAIDs Group ( $n = 70$ )		Exercise Group ( $n = 63$ )	NSAIDs Group ( $n = 58$ )	
Gender*	♂ 17:♀ 55	♂ 17:♀ 53	0.925	♂ 15:♀ 48	♂ 16:♀ 42	0.634
Age,** yrs	66.8 ± 12.8	68.9 ± 21.1	0.143	67.4 ± 13.4	71.2 ± 22.2	0.257
Height,** cm	154.6 ± 7.3	156.2 ± 7.5	0.837	154.5 ± 7.4	156.3 ± 7.3	0.575
Weight,** kg	59.4 ± 10.1	59.9 ± 10.7	0.581	59.3 ± 10.5	59.3 ± 9.5	0.713
BMI,** kg/m <sup>2</sup>	24.8 ± 3.5	24.5 ± 3.8	0.915	24.8 ± 3.6	24.3 ± 3.4	0.527

There is no statistically significant difference between the exercise group and the nonsteroidal antiinflammatory drugs (NSAIDs) group according to a  $\chi^2$  test\* and Student's *t* test.\*\*

of the NSAIDs group. The *P* value of JKOM was 0.038 with statistical significance, WOMAC was 0.102, SF-36 was 0.273, and VAS was 0.414 (Fig. 2, Table 3). The 95% confidence interval for the difference between the medians of the improvement rate (0–8 wk/0 wk) was from 0.008 to 0.248

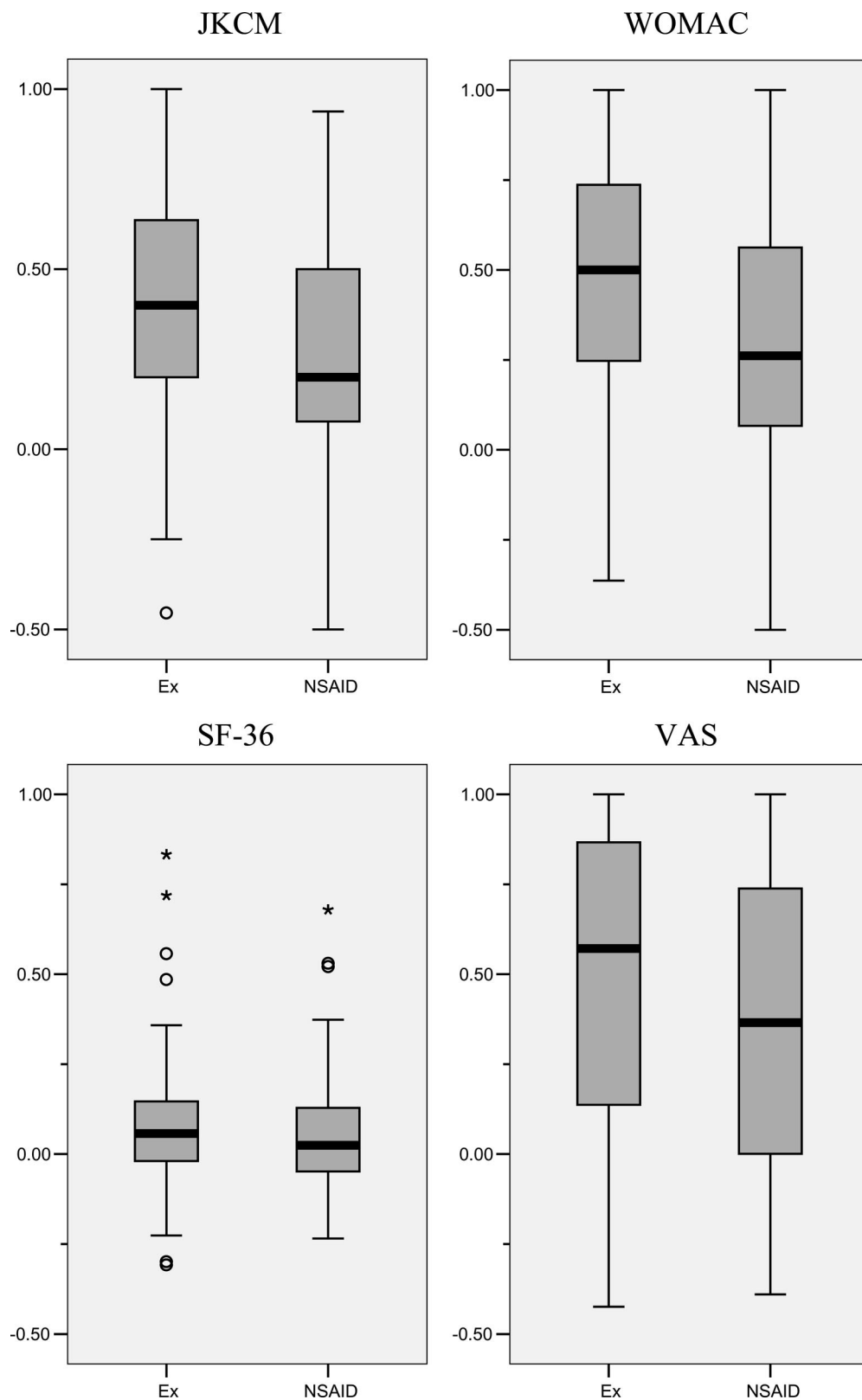
for JKOM, from –0.026 to 0.272 for WOMAC, from –0.025 to 0.272 for SF-36, and from –0.098 to 0.245 for VAS (Table 3). The lower confidence limits for the rates of improvement between baseline and 8 wks were more than 0% in JKOM, and more than –3% in WOMAC and

**TABLE 2** Comparison of the exercise and nonsteroidal antiinflammatory drug (NSAID) groups at the time of entry and at 8 wks

Time Course	Mean ± SD	Percentiles			Wilcoxon Signed Ranks Test	
		25th	50th (Median)	75th	Asymptotic Significance	95% Confidence Interval <sup>a</sup>
<b>Exercise</b>						
JKOM ( $n = 63$ )					<0.001**	–11.50 to –6.50
0 w	25.97 ± 16.19	14.0	19.00	37.00		
8 w	16.38 ± 14.30	6.00	11.00	23.00		
WOMAC ( $n = 63$ )					<0.001**	–11.46 to –6.25
0 w	22.85 ± 16.79	9.38	16.67	33.33		
8 w	13.69 ± 13.47	4.17	9.38	17.71		
SF-36 ( $n = 63$ )					0.001**	2.10 to 7.73
0 w	65.29 ± 15.91	53.18	66.18	78.91		
8 w	71.19 ± 16.33	61.09	74.18	83.27		
VAS ( $n = 61$ ), mm					<0.001**	–26.09 to –12.50
0 w	43.12 ± 25.38	18.94	47.00	60.78		
8 w	22.55 ± 20.68	4.33	17.51	37.74		
<b>NSAIDs</b>						
JKOM ( $n = 58$ )					<0.001**	–8.00 to –4.00
0 w	29.19 ± 18.07	15.00	25.00	39.00		
8 w	22.48 ± 18.00	9.00	18.50	33.25		
WOMAC ( $n = 58$ )					<0.001**	–9.38 to –3.65
0 w	25.95 ± 15.88	12.24	27.60	33.59		
8 w	18.59 ± 16.38	7.29	13.02	28.39		
SF-36 ( $n = 58$ )					0.023*	0.27 to 4.64
0 w	60.44 ± 15.98	47.23	59.41	72.41		
8 w	63.40 ± 16.36	50.16	65.55	78.05		
VAS ( $n = 56$ ), mm					<0.001**	–18.66 to –8.12
0 w	43.50 ± 22.23	23.00	39.95	60.48		
8 w	29.59 ± 23.94	10.30	23.64	49.84		

There were statistically significant differences between 0 wk and 8 wks in each score according to a Wilcoxon signed ranks test.\*\*\*

<sup>a</sup> The 95% confidence interval for the difference between two medians was also shown.



**FIGURE 2** Result of the improvement rate in each score.

SF-36. We were able to test “noninferiority” of the exercise treatment for knee osteoarthritis compared with NSAIDs in this particular clinical trial.

### Additional Treatments

Based on the Mann–Whitney  $U$  test, data from the treatment diaries of the subjects indicate that the

**TABLE 3** The difference in improvement rate of each score between the two groups

	Wilcoxon Signed Ranks Test		Percentiles			Asymptotic Significance	95% Confidence Interval <sup>a</sup>
	<i>n</i>	Average Rank	25th	50th (median)	75th		
JKOM						0.038*	0.008 to 0.248
Exercise	63	67.35	0.200	0.400	0.638		
NSAIDs	58	54.1	0.074	0.200	0.508		
WOMAC						0.102	-0.026 to 0.272
Exercise	63	66.0	0.120	0.469	0.714		
NSAIDs	58	55.57	0.061	0.262	0.580		
SF-36						0.273	-0.025 to 0.087
Exercise	63	64.35	-0.019	0.075	0.160		
NSAIDs	58	57.36	-0.052	0.024	0.129		
VAS						0.414	-0.098 to 0.245
Exercise	60	59.90	-0.047	0.484	0.865		
NSAIDs	54	54.83	-0.010	0.341	0.736		

There was a statistically significant difference between the exercise group and the nonsteroidal antiinflammatory drug (NSAID) group in Japanese Knee Osteoarthritis Measure (JKOM) score\* according to a Mann-Whitney *U* test. However, there was no statistically significant difference between the exercise group and the NSAIDs group in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and 36-Item Short-Form Health Survey (SF-36).

<sup>a</sup> The 95% confidence interval for the difference between two medians was also shown.

number of days used and the frequency of daily application of sticky pastes was not significantly different between groups. There was a clear trend that those who used plasters from the beginning of the study continued to use them, whereas those who did not use them from the outset remained nonusers for the duration of the study.

## DISCUSSION

The present trial conducted at the 35 study sites demonstrates that a 2-mo, home-based, quadriceps-strengthening exercise significantly decreased knee pain and improved daily activity and social participation. The exercise used in the present trial is no less effective than drug therapy with NSAIDs.

Previous studies have shown that therapeutic exercise for knee osteoarthritis can reduce knee pain and improve body functions.<sup>23-41</sup> Whereas previous research has revealed that various types of exercise have various degrees of statistically significant effectiveness on knee problems, the content of the studied therapeutic exercises have varied widely, from strengthening to aerobic and isokinetic exercise. In some trials, one exercise was often combined with another exercise. The majority of the trials also included other concomitant treatments, including use of medication, education, and other therapeutic techniques, which could be confounding factors for analysis. There have been no studies to compare home-based quadriceps-strengthening exercise with NSAIDs, to our knowledge.

We organized a very simple trial comparing one modest exercise and another established method. According to integrated data publications such as *BMJ Clinical Evidence*,<sup>1</sup> NSAIDs are an established and effective treatment in the short term (such as 2 mos). Despite the short-term efficacy, however, NSAIDs are reported to have a high incidence of adverse effects, mainly in the gastrointestinal tract, and possibly in promoting articular deterioration.<sup>4,9,14</sup>

We decided to choose home-based quadriceps exercise as the therapeutic procedure in this trial because this exercise is well accepted by many Japanese physicians. The physicians in our study have had much experience regarding conservative treatments of knee osteoarthritis. They have had an anecdotal awareness that patients who used knee exercises had high levels of satisfaction, despite actual improvements in muscle strength. Based on the expertise of the study authors, and on the feedback from other health care professionals, it was determined that prescribing home-based exercise would have a favorable result in terms of compliance and health improvement.

For the last several years, the quality of randomized controlled trials has been assessed using some methodological criteria. We have several issues regarding the design of this study that need to be addressed:

- (1) Because of technical limitations of the double-blind method, the present trial was an open-labeled study.

(2) Because Japanese patients, especially middle-aged or older ones, are not familiar with random allocation, we were afraid that they would refuse to follow the strengthening exercise alone for up to 8 wks. During discussions regarding selection of the study design protocol, some doctors expressed their concerns about lack of compliance by the patients to be allocated to the exercise group. Because of this limitation, it was decided that as an extra incentive to the patients, both groups would have access to sticky plasters on a voluntary basis. There was no statistically significant difference between the number of plaster users and the number of days using plasters between the exercise group and the NSAIDs group. We recognize that the use of plaster itself might have an effect, but we also know that the effectiveness of NSAIDs on osteoarthritis has been proved with previous evidence. Even if there is a possibility of a synergistic effect from plaster and oral drugs, the net effect found in the group with exercise and plaster is not less than that of the group with NSAIDs and plaster.

(3) Analytic presentation of data.

We mainly used nonparametric methods to analyze the data of this trial. The VAS score can be analyzed as a continuous parametric value. The SF-36 and WOMAC data can also be classified as parametric, but, from our analyses, we think that JKOM needs more careful handling.

Discussion about analytic methods for determining statistical significance is very important, especially in the case of nonparametric analysis and estimation of the 95% confidence interval for the difference between medians. In this trial, the final comparison of the improvement rate (0–8 wks/0 wk) was performed with a Mann–Whitney *U* test, associated with the estimation of the 95% confidence interval of the medians.<sup>21</sup>

Measuring health status or disease condition has been one of the most important efforts in medical practice. During the past several decades, a consensus has developed regarding the patient's point of view in measuring medical intervention. Patient-based outcome measures have recently been established as standardized tools to monitor the functioning and well-being of patients. Assessment of the direct effect of intervention—for example, quadriceps strength testing or timed up and go test—may be of value in outcome studies. However, our main target of intervention in this trial was the effect on daily activity or health-related quality of life—discomfort in symptoms, disability

in activities of daily living, and dissatisfaction in quality of life.

This approach does not advocate improving biomedical indicators or elucidating the pathomechanism of intervention; instead, it assesses the behavioral changes in patients by medical intervention using biopsychology, including patients' values and benefits.

Several mechanisms of therapeutic exercise for knee osteoarthritis have been proposed, such as muscle strengthening, pain reduction, improved general fitness, increased mobility and body balance, weight loss, and psychoemotional effect. The relationship between clinical effects and changes in these factors has not been confirmed yet. Therapeutic exercise, which is conducted by patients at home under appropriate management by an attending physician, is a suitable, self-control therapy for elderly people. To confirm the International Classification of Functioning, Disability and Health conceptual architecture,<sup>17</sup> further investigation is needed to make clear the biological mechanism of how exercise modifies quality-of-life outcomes and the relationship with clinical findings and change after 8 wks. When we prescribe a therapeutic method for patients, in whom effectiveness directly depends on their compliance to perform the therapy, we have to make up a system to improve or maintain patients' motivation. From our study, we have found that instructional documentation outlining the method of treatment for the patient, treatment notebooks that patients can use to record daily exercises and medications, and regular visits to a trusted clinic have the beneficial effect of maintaining compliance and improving health outcomes.

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