

Preliminary Results of Integrated Therapy for Patients With Knee Osteoarthritis

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Objective. To investigate the effects of integrated therapy on the functional status of patients with knee osteoarthritis (OA).

Methods. A total of 140 subjects with bilateral knee OA (Altman grade II) were randomized sequentially into 4 groups (groups I–IV). Group I received isokinetic exercises; group II received isokinetic exercise and pulse ultrasound for periarticular soft tissue pain; group III received isokinetic exercise, pulse ultrasound, and intraarticular hyaluronan therapy; and group IV acted as the control group. The therapeutic effects of the interventions were evaluated by changes in Lequesne's index, knee range of motion, peak muscle torques of knee flexion and extension, and ambulation speed after 8 weeks of treatment and at followup 1 year later. In addition, changes in visual analog scale pain and rates of attrition in each group were also recorded.

Results. Patients in groups I–III exhibited increased muscle peak torques and significantly reduced pain and disability after treatment and at followup. Groups II and III showed significant improvements in range of motion and ambulation speed after treatment. Group III also showed the greatest increase in walking speed and decrease in disability after treatment and at followup. Both group II and group III had significant gains in muscular strength after treatment and at followup; group III showed the greatest gains.

Conclusion. An integrated therapy deals with the extra- and intraarticular progressive pathologic changes, and kinesiologic management of OA is suggested for the management of knee OA.

KEY WORDS. Osteoarthritis; Isokinetic exercise; Ultrasound; Hyaluronan therapy.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent disease associated with significant morbidity, and is one of the most common causes of functional limitation and dependency. OA of the knee is particularly disabling due to symptoms such as pain, stiffness, and muscle weakness (1,2). Furthermore, restricted joint range of motion (ROM) is associated with abnormal posture and may exacerbate disability (3).

OA is characterized by noninflammatory deterioration

of the articular cartilage with reactive new bone formation at the joint's surface and margins. Many studies (4–6) have indicated that the primary lesion of OA is in the articular cartilage, in which the earliest change is diminution of mucopolysaccharide and chondroitin sulfate relative to the collagen in the matrix, thereby unmasking the collagen. Normally, the matrix dissipates stresses hydrostatically; but when the collagen is unmasked, its fibers are subjected to excessive flexural and torsional stresses, leading to rupture and the lesions characteristic of OA. Therefore, early prevention of matrix diminution and induction of matrix synthesis by chondrocytes is important, as well as decreasing the resistance of joint ROM.

Hyaluronic acid (HA), a major component of synovial fluid (SF) and cartilage, is a high molecular weight polysaccharide made of long nonsulfated straight chains of variable disaccharide lengths composed of N-acetylglucosamine and glucuronic acid. HA plays a number of key roles in the trophic status of the cartilage and in the regulation of the intraarticular environment. The physiologic and pharmacologic properties of HA have recently been reviewed (7–11). Its unique viscoelastic properties confer remarkable shock-absorbing and lubricating abilities to SF,

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while its enormous macromolecular size and hydrophilicity serve to retain fluid in the joint cavity during articulation. In addition, HA can form a pericellular coat around cells; interact with proinflammatory mediators; and bind to cell receptors to modulate cell proliferation, migration, and gene expression. In OA, however, the molecular weight and concentrations of HA are reduced. Therefore, HA therapy is indicated for controlling intraarticular conditions during therapeutic exercises for knee OA.

Cartilage is an avascular tissue, and the chondrocytes within it depend on diffusion and convection for nutrition. The health of cartilage depends in part on the mechanical load it receives. This process is enhanced by the cyclic loading induced by everyday activities that produce deformations, pressure gradients during ROM of the joints, and fluid flows within the tissues. Moderate to strenuous articular loading, such as that associated with regular distance running, seems to have no adverse effects on the health of normally congruent joints. However, normal loads can also accelerate degeneration in deformed, unconstrained, or damaged joints due to the instability of the arthritic joint and uneven loading forces (12). Therefore, increasing the stability of an arthritic joint prevents further deterioration. Quadriceps femoris weakness, associated with thigh muscle wasting, is an important factor in knee OA because the earliest description and treatment of OA traditionally include exercises specifically intended to increase quadriceps strength (5,13) thereby reducing joint instability.

Several recent longitudinal studies have concluded that carefully controlled exercise programs, designed primarily to address OA of the knee, are indeed beneficial (14,15). Reported benefits include increased joint mobility, increased strength, and enhanced performance in sports activities. However, patient compliance is an issue, and studies with higher rates of compliance produced better results. Patient compliance depends on many elements, including consistent education, encouragement, and followup. Injury and complications as direct consequences of inappropriate exercise (16), such as periarticular soft tissue pain during muscle strengthening exercises and resistance during ROM exercises, are the major causes of poor compliance.

Therapeutic ultrasound (US) has been used to treat many musculoskeletal diseases, and is reputed to reduce edema, relieve pain, increase the ROM (17–21), and accelerate joint tissue repair. In reviewing the effectiveness of US in treating musculoskeletal conditions, Falconer et al (17) found that most reports revealed that therapeutic US appears to relieve OA pain. Some investigations have applied US to enhance the flexibility of connective tissues (20). However, few reports have discussed the effects of US on intraarticular injection of HA or therapeutic exercise for OA.

Therefore, in this study we compared the effects of integrated therapy, which included isokinetic muscle strengthening exercise, periarticular soft tissue pain control (US), and intraarticular therapy (HA), and other combination treatments on the functional status of patients with knee OA.

PATIENTS AND METHODS

Patients. A total of 140 patients with bilateral moderate knee OA (Altman grade II) (22) were selected and randomly assigned to 4 groups (groups I–IV) by a secure system of opaque sealed envelopes that were sequentially numbered I–IV. The doctor who assigned the patients was blinded to the treatment the patients would receive. Patients in each group received various treatments 3 times weekly for 8 weeks. Patients in group I (35 patients) received isokinetic muscular strengthening exercises; those in group II (35 patients) received isokinetic exercise and pulse US treatment for painful periarticular soft tissue; those in group III (35 patients) received isokinetic exercise, pulse US treatment for painful periarticular soft tissue, and intraarticular hyaluronan therapy; and those in group IV (35 patients) acted as controls who received no treatment other than warmup exercises. Patients in all groups received a warmup exercise with 20 minutes of hot packs and underwent passive ROM exercises on an electric stationary bike (20 cycles per minute) for 5 minutes to both knees before undergoing muscle strengthening exercises. The therapeutic effects of these exercises were evaluated by changes in the ROM of the arthritic knee (23), visual analog scale (VAS) (24), Lequesne's index (LI) (25) (Table 1), ambulation speed (AS), and muscle peak torques (MPT) of knee flexion and extension measured by means of an isokinetic dynamometer (Kin-Com; Chattanooga Corporation, Chattanooga, TN) (26) before treatment, after treatment, and at followup 1 year later. Compliance with the prescribed exercise program in each group was also analyzed after complete treatment. All the evaluations were performed by the same physiatrists who were also blinded to the treatment the patients received. All participants gave informed consent for the study, and the study protocol was approved by the Ethical Review Committee of Kaohsiung Medical University.

Measurement of knee ROM. The active ROM was measured with a large, plastic goniometer with 25-cm movable double arms, marked in 1-degree increments. This device is reportedly reliable if the patient remains in one position for all measurements (23). Measurement of knee flexion was performed in the supine position by simultaneously flexing the hip and knee, with the foot on the measured side resting on the table as far as possible. The opposite leg was kept extended on the table. Knee extension was also measured with patients lying supine on an examination couch with the leg kept straight, and the examiner supported the weight of the leg as the patient moved. The fully extended knee was considered zero position, and the degrees of maximum flexion, maximum extension, and extension deficit, when present, were recorded. A negative ROM score for extension indicated that the patient was unable to reach the zero position. The angle between maximum flexion and maximum extension was described as the excursion range.

Measurement of pain severity. The severity of knee pain was evaluated by the VAS after patients had re-

Table 1. Lequesne's functional index for knee OA*

	Points
Pain	
Nocturnal pain	
Only on movement or in certain attitudes	1
Even without moving	2
Morning stiffness or pain after getting up	
Less than 15 minutes	1
15 minutes or more	2
A standing position within 30 minutes, resulting in more pain	1
When walking, does the pain occur	
Only after a certain distance	1
From the beginning, and does it increase	2
Pain or discomfort when getting up from a seat	1
Maximum distance walked	
More than 1 km, but limited	1
About 1 km (about 15 minutes)	2
From 500 to 900 m (about 8–15 minutes)	3
From 300 to 500 m	4
From 100 to 300 m	5
Less than 100 m	6
With 1 walking stick or crutch	+1
With 2 walking sticks or crutches	+2
Some difficulties in daily life	
Can you ascend a flight of stairs?	0–2
Can you go down a flight of stairs?	0–2
Can you arrange something on a low shelf while squatting or being on your knee?	0–2
Can you walk on unequal ground?	0–2
Are you suffering from shooting pains and/or sudden lack of support in the involved limb?	
Sometimes	1
Often	2
* Answer rating: easily = 0; with difficulty = 1 (or 0.5 or 1.5); impossible = 2. The disability may be graded as follows: >14 points = extremely severe; 11–13 points = very severe; 8–10 points = severe; 4–7 points = moderate; 1–3 points = mild. Less than 7 points means acceptable status for isokinetic exercise.	

mained in a weight-bearing position (walking or standing) for 5 minutes. The instrument consisted of 10-cm horizontal or vertical lines, with anchor points of 0 (no pain) and 10 (maximum pain).

Measurement of disability. Disability of patients with OA of the knee was evaluated with LI. The questionnaire included 11 questions regarding knee discomfort, endurance of ambulation, and difficulties in daily life (25). A maximum score of 26 indicated the greatest degree of dysfunction, and a score of 1–3 indicated mild dysfunction. A score <7 points indicated that the patient had functional status acceptable for isokinetic exercise (15).

Measurement of ambulation speed. AS was evaluated by the time spent walking for a predetermined distance. A distance of 50 meters was preset on the treadmill, and the patient walked on the treadmill at a self-selected pace without instruction to cover the distance as quick as they

could, and an alarm sounded when the 50 meters was completed, although the patient kept walking briefly to cool down. The walking time was recorded with a stopwatch by the same physiatrist.

Measurement of isokinetic peak torque of knee flexion and extension. To evaluate the maximum voluntary force capacity, the peak torque of the arthritic knee was measured using a modified form of the method used by Snow and Blacklin (26) in the following steps: knee extension with concentric quadriceps contraction (Ex/Con), knee flexion with eccentric quadriceps contraction (Flex/Ecc), knee flexion with concentric biceps femoris contraction (Flex/Con), and knee extension with eccentric biceps femoris contraction (Ex/Ecc). Patients were seated leaning against a backrest inclined at 16° from the vertical and with the seat inclined 6° from the horizontal. The axis of the knee was aligned with the axis of the Kin-Com 505 (Chattanooga Corporation) exercise arm; accuracy of alignment was checked by allowing the patient to extend the leg while pushing against the shin pad positioned over the lower third of the leg. If the pad did not move up or down the leg over the ROM to be tested, the knee was considered to be aligned with the axis of the exercise arm. Gravity-compensated torque values were corrected with the exercise arm positioned 15° from the horizontal.

The Kin-Com's exercise arm was used to set the test ROM. The angle at which knee flexor muscle shortening began (start angle) was set at 20° from the horizontal, and the angle at which muscle lengthening began (return angle) was set at 85° from the horizontal. To calculate torque, the distance between the point of application of the generated force and the axis of rotation of the exercise arm was measured using the scale on the arm itself and was keyed into the computer. Each patient used the same radius for all tests. Exercise-arm velocity was set to 60°/second and 180°/second, respectively, for the above isokinetic peak torque measurements, and mean peak torque was an average of 3 times the measurements.

Isokinetic exercise. Isokinetic exercise is a mode of speed-constant exercise. The velocity of joint motion is constant, excluding acceleration to and deceleration from the designated speed, and the force is dependent upon how hard the individual pushes against the load cell.

After evaluation of pain and ROM of each arthritic joint, and measurement of blood pressure and heart rate, stretching of quadriceps and hamstrings followed the application of hot packs. The patient then underwent a 5-minute warmup exercise on a stationary bike set without resistance. The isokinetic muscle-strengthening exercise program was performed, as described in our previous study (15), for left and right knees 3 times a week for 8 weeks (24 sessions). The isokinetic exercise program began with 60% of the mean peak torque preset in the Kin-Com, and the patient reached the preset intensity by visual biofeedback. An increasing dose program was used in the first 5 sessions (1 set to 5 sets), and a dose of 6 sets was applied from the sixth to twenty-fourth sessions, with the density rising from 60% to 80% of the mean peak torque as the patient was able. Each set consisted of 5 repetitions of concentric

Table 2. Knee ROM in each group before and after treatment*

	I	II	III	IV
Before	103 ± 13 (70)	104 ± 10 (70)	103 ± 12 (70)	101 ± 13 (70)
After	108 ± 17 (60)†	114 ± 15 (64)‡	120 ± 13 (68)‡	98 ± 10 (64)
ROM	5 ± 10†	10 ± 14†	16 ± 15§	-4 ± 13
Followup	110 ± 14 (52)†	118 ± 14 (58)†	124 ± 18 (64)§	98 ± 17 (56)

* Values are the mean ± SD (number of knees in each group at various times intervals). ROM = range of motion.
† Significant difference in Lequesne's Index (LI) in each group compared with the control group at various time intervals ($P < 0.05$).
‡ Significant difference in LI in each group after treatment and compared with the control group at various time intervals ($P < 0.05$).
§ Significant difference in LI in each group compared with the control group at various time intervals and compared with other treated groups ($P < 0.05$).

(Con/Ecc) contraction in angular velocities of 30°/second and 120°/second for extensors, and 5 repetitions of eccentric and concentric (Ecc/Con) contractions in angular velocities of 30°/second and 120°/second for flexors. The start and stop angles for extension exercise were 40° and 70°, and the start and stop angles for flexion exercise were 70° and 40°. Patients were allowed 5 seconds of rest between sets, 10 seconds of rest between extensors and flexors strengthening modes, and 10 minutes of rest between right and left knee training.

Ultrasound treatment. *The locations of sonication (ultrasound treatment).* The regions for application of US were selected according to locations of tendopathy, enthesopathy, or cystitis indicated by the real time 5–12-MHz high-resolution linear scanner (HDI 1500; Advanced Technologies Laboratories, Bethell, WA) followed by tender point findings made during orthopedic examination. The most common periarticular soft tissue lesions included anserine bursitis, medial collateral enthesitis, popliteal tendonitis, Baker's cyst, and supra- and infrapatellar bursitis.

Pulse sonication. The US (Sonopulus 590; Enraf Nonius, AL Delft, Netherlands) had a frequency of 1 MHz and a spatial and temporal peak intensity of 2.5 Watts/cm², and pulsed at a duty cycle of 25%. Sonication was performed 3 times a week for 8 weeks. The US probe was applied for 5 minutes to each treated region over the medial collateral ligament, anserine bursa, and the popliteal fossa tender points, a total treated area of ~25 cm². The patient was kept in a supine position with bilateral knee flexion of 90° for medial collateral ligament and anserine bursa, and in a prone position with bilateral knee full extension for treatment of the popliteal fossa tender points. The intensity of sonication was adjusted to the level at which the patient experienced a warm sensation or a mild sting.

Intraarticular hyaluronan injection. The patients in group III received intraarticular injections of sodium hyaluronate (Hyalgan 20 mg in 2 ml of phosphate buffer [Fidia S.P.A., Abano Terme, Italy], extracted from rooster combs, pyrogen free, mean molecular weight 630,000 daltons) every 7 days for 5 weeks as the usual treatment course for HA (27).

Rate of attrition. The rate of attrition was determined by participants who dropped out of the treatment course. The major causes of dropout were also analyzed.

Home program exercise routine. After completing treatment, patients in treated groups received a home exercise program with 15 minutes of stationary bicycling exercise, using an exercise bike or a common bicycle with a device attached to elevate the posterior wheel to execute/perform the bicycling exercise for patients who did not have an exercise bike at home.

Statistical analysis. Paired *t*-test was used to study the changes in VAS, LI, AS values, and peak torques in each group immediately after treatment and at followup 1 year later. One-way analysis of variance with Tukey's test was used to compare the differences in VAS, LI, AS, and peak torques between 3 treated groups, and Dunnett's test was used to compare the difference between treated groups and the control group at zero time, after treatment, and 1 year later. A statistically significant difference was defined as $P < 0.05$.

RESULTS

Participants. The 140 patients ranged from 40 to 77 years old (mean age 65.0 ± 6.4), with a female:male ratio of 113:27. The duration of knee pain ranged from 5 months to 12 years.

Changes in range of motion. The changes in average ROM of the arthritic knees for each group are shown in Table 2. Nine patients stopped the therapeutic exercises due to intolerable pain during exercise (5 patients in group I, 3 in group II, and 1 in group III). Contact with 13 patients was lost during the followup period (4 patients in group I, 3 in group II, 2 in group III, and 4 in the control group). The average ROM of each group was initially similar, but ROM scores later increased significantly in all treated groups, with patients in group III showing the greatest improvement of ROM, both after treatment and in the followup period.

Table 3. Average VAS score for knee pain in each group before and after treatment*

	I	II	III	IV
Before	5.3 ± 1.5 (70)	5.5 ± 1.7 (70)	5.6 ± 1.4 (70)	5.4 ± 1.7 (70)
After	4.1 ± 0.6 (60)†	3.0 ± 1.8 (64)†	2.5 ± 1.6 (68)‡	4.9 ± 1.2 (64)
VAS	1.2 ± 1.6	2.5 ± 1.9	3.1 ± 1.8§	0.5 ± 1.7
Followup	3.9 ± 1.4 (52)†	2.6 ± 1.5 (58)¶	2.0 ± 1.3 (64)#	6.6 ± 1.5 (56)**

* Values are the mean ± SD (number of knees in each group at various times intervals). VAS = visual analog scale.
† Significant difference in VAS score in each group after treatment and compared with the control group at various time intervals ($P < 0.05$).
‡ Significant difference in VAS score in each group after treatment, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).
§ Significant difference compared with other treated groups ($P < 0.05$).
¶ Significant difference in VAS score in each group between after treatment and those at followup, and compared with the control group at various time intervals ($P < 0.05$).
Significant difference in VAS score in each group between after treatment and those at followup, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).
** Significant difference in VAS score in each group between after treatment and those at followup ($P < 0.05$).

Changes in knee pain. The changes in average scores for knee pain in each group are shown in Table 3. Pain scores for groups I–IV were initially similar, but pain scores decreased significantly in all treated groups, and pain scores had continued to decrease significantly in groups II and III at the followup, whereas pain scores increased in the controls. Patients in group III showed the greatest degree of pain reduction, both after treatment and in the followup period.

Changes in LI. Initially, the treated and control groups showed no significant LI differences. However, average LI scores decreased significantly in all treated groups after treatment, and at the 1-year followup. Patients in group I had the least reduction in LI scores after treatment, and patients in group III had the greatest reduction in disability after treatment and during the followup period. The changes in mean LI values in each patient group are shown in Table 4.

Changes in AS. The mean changes in AS in each group are shown in Table 5. Initially, the average AS did not differ markedly between treated and control groups, but the average AS increased significantly in groups II and III after treatment. The average AS increased in all treated groups at followup when compared with the controls, with patients in group III showing the most improvement in AS, and patients in group I showing the least improvement, both after treatment and at the followup.

Changes in muscle power. The changes in mean peak torques of knee flexion and extension in concentric and eccentric contraction in all patient groups are shown in Table 6 (60°/second) and Table 7 (180°/second). The average peak torques of 60°/second in Ex/Con, Ex/Ecc, Flex/Ecc, and Flex/Con increased significantly in all treated groups, both after treatment and at the followup. Patients in group I showed the least improvement in peak torques

Table 4. Average LI of patients in each group before and after treatment*

	I	II	III	IV
Before	7.6 ± 1.2 (35)	7.4 ± 1.6 (35)	7.5 ± 1.3 (35)	7.4 ± 1.1 (35)
After	6.1 ± 0.9 (30)†	4.4 ± 1.1 (32)†	4.0 ± 0.7 (34)‡	6.9 ± 1.3 (32)
LI	1.5 ± 1.4§	3.1 ± 1.8§	3.5 ± 1.7¶	0.5 ± 1.7
Followup	5.8 ± 1.8 (26)†	3.3 ± 1.5 (29)#	2.5 ± 1.6 (32)**	8.1 ± 1.5 (28)††

* Values are the mean ± SD (number of patients in each group at various times). LI = Lequesne's index.
† Significant difference in LI in each group after treatment and compared with the control group at various times intervals ($P < 0.05$).
‡ Significant difference in LI in each group after treatment, compared with the control group at various times intervals, and compared with other treated groups ($P < 0.05$).
§ Significant difference in LI in each group compared with the control group at various times intervals ($P < 0.05$).
¶ Significant difference in LI in each group compared with the control group at various times intervals and compared with other treated groups ($P < 0.05$).
Significant difference in LI score in each group between after treatment and those at followup and compared with the control group at various time intervals.
** Significant difference in LI score in each group between after treatment and those at followup, compared with the control group at various times intervals, and compared with other treated groups ($P < 0.05$).
†† Significant difference in LI score in each group between after treatment and those at followup ($P < 0.05$).

Table 5. Average AS of patients in each group before and after treatment*

	I	II	III	IV
Before	72.6 ± 6.1 (35)	71.3 ± 6.7 (35)	72.4 ± 4.8 (35)	73.9 ± 2.4 (35)
After	82.9 ± 5.3 (30)†	90.2 ± 3.1 (32)‡	95.6 ± 2.7 (34)‡	75.8 ± 3.9 (32)
AS	10.2 ± 9.7†	20.3 ± 9.5	24.8 ± 8.6	2.0 ± 7.7
Followup	85.3 ± 6.5 (26)§	94.3 ± 6.8 (29)§	99.3 ± 6.8 (32)¶	70.1 ± 5.1 (28)

* Values are the mean ± SD (number of patients in each group at various time intervals). AS = ambulation speed (meters/minute).
† Significant difference compared with other treated groups ($P < 0.05$).
‡ Significant difference in AS in each group after treatment and compared with the control group at various time intervals ($P < 0.05$).
§ Significant difference in AS of each group compared with the control group at various time intervals ($P < 0.05$).
¶ Significant difference in AS of each group compared with the control group at various time intervals and compared with other treated groups ($P < 0.05$).

after treatment, but group I patients still showed significant improvements in MPT when compared with the control group at followup. Group III had the greatest improvement in peak torque at 180°/second in all contraction modes (Ex/Con, Ex/Ecc, Flex/Con, and Flex/Ecc) after treatment and at followup.

Attrition rate. The rate of attrition was 14% (5 of 35) in group I, 9% (3 of 35) in group II, 3% (1 of 35) in group III, and 9% (3 of 35) in the control group. Reasons for withdrawal from the treatment included intolerable knee pain (75% [9 of 12]) induced by the prescribed exercises and leg muscle weakness.

DISCUSSION

Clinical OA is the consequence of a breakdown in the joint's normal function, which in turn is associated with altered anatomy. There is loss of freedom for the articulating surfaces to move over one another easily and a loss of joint stability. The loss of freedom of motion is associated with loss of articular cartilage, a change in joint shape, and alterations in the ligamentous support and neuromuscular control. Therefore, malfunction of an arthritic joint may result from acute or chronic injuries that produce either anatomic alterations in the shape of the articulating surface, loss of integrity of the support structures around the joint, or alterations in the mechanical properties of the tissue matrices that make up the joint. OA is not a simple wear-and-tear phenomenon, but an active process that is part of the reparative response to injury. It is reasonable to postulate that such a process might be manipulated to produce beneficial or detrimental effects on joint function and symptoms. Therefore, an integrated therapy of multiple interventions concentrating on the arthro-protective functioning of the total joint including intraarticular, periarticular, and kinesiological management is indicated. The results showed that patients in group III who received more than triple therapy had the best gain in functional improvement.

Pain in the osteoarthritic knee may be due to several conditions, including loss of articular cartilage; mechanical compression of either the medial knee compartment with varus deformity or the lateral compartment with val-

gus deformity; stretching of medial or lateral collateral ligaments; micro fractures and subchondral fractures; capsular distension by effusion; and patellar and associated syndromes such as anserine bursitis or prepatellar bursitis. Furthermore, the interaction of these factors results in vicious changes of intraarticular and periarticular connective tissues.

Periarticular connective tissue is composed of collagen fibers within a proteoglycan matrix. The tissue may become fibrotic, contracted, or shortened when subjected to immobilization or inactivity due to arthritic joint pain, resulting in joint capsule contractures and a limited ROM. Adaptive shortening of the muscles may also occur, with muscles immobilized in a shortened position demonstrating shortening within a week. After 3 weeks in this shortened position, the loose connective tissue in the muscle becomes dense connective tissue, and a fixed muscle contracture develops (28), resulting in instability of the joint. However, through an appropriate physical modality, such as the US used in the present study, the patients in groups II and III manifested the greatest improvement in MPT and the least disability, which were correlated closely with an increased ROM after periarticular soft tissue pain control.

A number of other factors have been proposed as possible explanations for the level of disability in patients with knee OA, including physical factors such as the reduced ROM of the knee joints. In a study of elderly Swedish patients (29), strong correlations were found between knee and hip joint ROM and disability. Odding et al (30) found that restricted flexion of the knees was a strong risk factor for locomotor disability in activities primarily involving the lower extremities, such as walking, climbing stairs, and rising from and sitting down in a chair. Steultjens et al (31) reported that restricted joint mobility, especially in flexion of the knee, appears to be an important determinant of disability in patients with OA.

The major causes of ROM limitation of the arthritic knee are joint pain and weakness of the quadriceps (31), which is one of the key muscles controlling the stability of the arthritic knee. Our previous study (15) showed that although isokinetic strengthening exercise had the greatest therapeutic effect on the functional status of patients with knee OA, it also had the lowest level of compliance with treatment when compared with isotonic or isometric exer-

Table 6. Mean peak torque of knee flexion and extension in concentric and eccentric contraction at 60°/second in each group before and after treatment*

	I	II	III	IV
60° (Ex/Con)				
Before	230.4 (70)	232.7 (70)	230.4 (70)	229.3 (70)
After	250.8 (60)†	293.5 (64)‡	326.1 (68)§	225.1 (64)
MPT	20.3	60.8	95.3¶	-4.2
Followup	273.3 (52)#	346.5 (58)**	380.1 (64)††	211.3 (56)
60° (Ex/Ecc)				
Before	425.3 (70)	423.7 (70)	428.9 (70)	426.3 (70)
After	465.5 (60)‡	504.1 (64)‡	561.3 (68)§	424.7 (64)
MPT	40.4	80.3	132.1¶	-1.5
Followup	485.1 (52)#	557.3 (58)**	627.4 (64)††	400.4 (56)
60° (Flex/Con)				
Before	276.3 (70)	273.1 (70)	278.2 (70)	270.7 (70)
After	296.4 (60)#	322.0 (64)‡	357.9 (68)§	260.8 (64)
MPT	22.0	49.3	80.9¶	-10.3
Followup	286.3 (52)#	353.7 (58)**	392.1 (64)††	230.0 (56)‡‡
60° (Flex/Ecc)				
Before	335.3 (70)	344.5 (70)	338.8 (70)	341.1 (70)
After	365.5 (60)#	406.6 (64)‡	458.3 (68)§	330.5 (64)
MPT	30.1	62.0	80.51¶	-10.6
Followup	375.6 (52)#	420.3 (58)#	473.6 (64)§§	290.3 (56)‡‡
<p>* Values are the mean (number of knees in each group at various time intervals). Ex/Con = knee extension with concentric quadriceps contraction; MPT = mean peak torque; Ex/Ecc = knee extension with eccentric biceps femoris contraction; Flex/Con = knee flexion with concentric biceps femoris contraction; Flex/Ecc = knee flexion with eccentric quadriceps contraction.</p> <p>† Significant difference in peak torque in each group after treatment ($P < 0.05$).</p> <p>‡ Significant difference in peak torque in each group after treatment and compared with the control group at various time intervals ($P < 0.05$).</p> <p>§ Significant difference in peak torque in each group after treatment, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).</p> <p>¶ Significant difference compared with other treated groups ($P < 0.05$).</p> <p># Significant difference in peak torque in each group compared with the control group at various time intervals ($P < 0.05$).</p> <p>** Significant difference in peak torque in each group between after treatment and those at followup, and compared with the control group at various time intervals ($P < 0.05$).</p> <p>†† Significant difference in peak torque in each group between after treatment and those at followup, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).</p> <p>‡‡ Significant difference in peak torque in each group between after treatment and those at followup ($P < 0.05$).</p> <p>§§ Significant difference in peak torque in each group compared with the control group at various time intervals and compared with other treated groups ($P < 0.05$).</p>				

cises, due to exercise-induced knee pain. Patients in groups II and III had better compliance than those in group I, which was compatible with the decrease of pain and increase of ROM after undergoing US treatment and hyaluronan intraarticular therapy.

Isokinetic MPT at 60°/second and 180°/second were measured to determine the changes in MPT. Greater MPT improvements were seen in both groups II and III (Tables 6 and 7). However, the improvement of MPT was significantly greater in group III than in group II, which was compatible with the improvements in ROM, AS, and reduction in VAS and LI. This implies that intraarticular hyaluronan therapy could further enhance the therapeutic effects of US and isokinetic exercise.

Studies using large animal models of OA have shown that HAs with molecular weights (MW) within the range of 0.5×10^6 – 1.0×10^6 daltons were generally more effective in reducing indices of synovial inflammation and restoring the rheologic properties of synovial fluid than HAs with MW of more than 2.3×10^6 daltons (32). These experi-

mental findings are consistent with light and electron microscopic studies of synovial membrane and cartilage biopsy specimens obtained from patients with OA who received 5 weekly intraarticular injections of HA (MW = 0.5×10^6 – 0.73×10^6 daltons), in which evidence of partial restoration of normal joint tissue metabolism was observed (33). Furthermore, by mitigating the activities of proinflammatory mediators and pain-producing neuropeptides released by activated synovial cells, HA may reduce the symptoms of OA. The partially restored synovial fluid rheologic properties and synovial fibroblast metabolism seen in animal models are compatible with the results of joint pain reduction and improvement of functional status (34).

According to Lequesne's functional index, disability may be graded by the scoring as follows: >14 points = extremely severe; 11–13 points = very severe; 8–10 points = severe; 4–7 points = moderate; 1–3 points = mild (as shown in Table 1). The presented results implied that an approximately 3-point reduction of LI (from mod-

Table 7. Mean peak torque of knee flexion and extension in concentric and eccentric contraction at 180°/second in each group before and after treatment*

	I	II	III	IV
180° (Ex/Con)				
Before	181.5 (70)	183.3 (70)	180.1 (70)	182.3 (70)
After	204.8 (60)†	256.3 (64)†	285.3 (68)‡	179.7 (64)
MPT	23.3	73.0	104.3§	-3.6
Followup	214.6 (52)¶	270.1 (58)¶	305.4 (64)#	160.7 (56)
180° (Ex/Ecc)				
Before	475.6 (70)	473.3 (70)	480.1 (70)	478.7 (70)
After	565.1 (60)†	633.3 (64)†	683.3 (68)‡	460.3 (64)
MPT	90.5	163.1	203.7§	-16.2
Followup	583.3 (52)¶	675.7 (58)¶	736.7 (64)#	421.6 (56)**
180° (Flex/Con)				
Before	180.3 (70)	182.4 (70)	183.1 (70)	180.4 (70)
After	215.7 (60)†	267.9 (64)†	299.5 (68)‡	164.3 (64)
MPT	35.7	85.3	116.2§	-16.0
Followup	225.3 (52)†	317.3 (58)††	361.3 (64)#	151.2 (56)**
180° (Flex/Ecc)				
Before	310.3 (70)	309.2 (70)	314.3 (70)	306.2 (70)
After	335.3 (60)¶	384.1 (64)†	419.7 (68)‡	294.1 (64)
MPT	25.0	75.6	105.2§	-12.1
Followup	345.3 (52)¶	414.5 (58)¶	456.2 (64)#	277.3 (56)**
<p>* Values are the mean (number of knees in each group at various time intervals). Ex/Con = knee extension with concentric quadriceps contraction; MPT = mean peak torque; Ex/Ecc = knee extension with eccentric biceps femoris contraction; Flex/Con = knee flexion with concentric biceps femoris contraction; Flex/Ecc = knee flexion with eccentric quadriceps contraction.</p> <p>† Significant difference in peak torque in each group after treatment and compared with the control group at various time intervals ($P < 0.05$).</p> <p>‡ Significant difference in peak torque in each group after treatment, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).</p> <p>§ Significant difference compared with other treated groups ($P < 0.05$).</p> <p>¶ Significant difference of peak torque in each group compared with the control group at various time intervals ($P < 0.05$).</p> <p># Significant difference in peak torque in each group between after treatment and those at followup, compared with the control group at various time intervals, and compared with other treated groups ($P < 0.05$).</p> <p>** Significant difference in peak torque in each group after treatment ($P < 0.05$).</p> <p>†† Significant difference in peak torque in each group between after treatment and those at followup, and compared with the control group at various time intervals ($P < 0.05$).</p>				

erate-severe disability to mild-moderate) in groups II and III after treatment had a relative 20-meters/minute improvement in AS, >2.5 VAS pain score reduction in joint pain, and ~10° ROM improvement in arthritic joints.

In comparing the data upon completing the treatment and at followup, we found that there were further decreases of joint pain and increases of MPT in groups II and III; however, there were no further changes in ROM and AS. The results demonstrated that bicycling after completing treatment maintained or even improved the effects during the followup periods.

In conclusion, an integrated therapy including US, isokinetic strengthening exercise, and intraarticular hyaluronan therapy that deals with the intraarticular and extraarticular progressive pathologic changes of knee OA is suggested for the management of knee OA.

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