ORIGINAL ARTICLE

Nonsteroidal Anti-Inflammatory Drug or Glucosamine Reduced Pain and Improved Muscle Strength With Resistance Training in a Randomized Controlled Trial of Knee Osteoarthritis Patients

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ABSTRACT. Petersen SG, Beyer N, Hansen M, Holm L, Aagaard P, Mackey AL, Kjaer M. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. Arch Phys Med Rehabil 2011;92:1185-93.

Objectives: To investigate the effect of 12 weeks of strength training in combination with a nonsteroidal anti-inflammatory drug (NSAID), glucosamine, or placebo on muscle cross-sectional area (CSA), strength (primary outcome parameters), and function, power, pain, and satellite cell number (secondary outcome parameters) in patients with knee osteoarthritis (OA).

Design: Double-blinded, randomized controlled trial.

Setting: Hospital.

Participants: Patients (N=36; 20 women, 16 men; age range, 50–70y) with bilateral tibiofemoral knee OA. A total of 181 patients were approached, and 145 were excluded.

Interventions: Patients were randomly assigned to treatment with the NSAID ibuprofen (n=12), glucosamine (n=12), or placebo (n=12) during 12 weeks of quadriceps muscle strength training.

Main Outcome Measures: Muscle CSA and strength.

Results: No differences between groups were observed in gains in muscle CSA. Training combined with ibuprofen increased maximal isometric strength by an additional .22Nm/kg (95% confidence interval [CI], .01–.42; $P=.04$), maximal eccentric muscle strength by .38Nm/kg (95% CI, .05–.70; $P=.02$), and eccentric muscle work by .27J/kg (95% CI, .01–.53; $P=.04$) in comparison with placebo. Training combined with glucosamine increased maximal concentric muscle work by an additional .24J/kg versus placebo (95% CI, .06–.42; $P=.01$).

Conclusions: In patients with knee OA, NSAID or glucosamine administration during a 12-week strength-training program did not improve muscle mass gain, but improved maximal muscle strength gain in comparison with treatment with placebo. However, we do not find that the benefits are large enough to justify taking NSAIDs or glucosamine.

Key Words: Dietary supplements; Exercise; Ibuprofen; Rehabilitation; Satellite cells; skeletal muscle.

OSTEOARTHRITIS (OA) IS THE most common joint disease, affecting not only the joints but also the surrounding muscles, which become weak.[1] Reduced quadriceps strength appears to be a risk factor as well as a consequence of OA of the knee.[2-5] Exercise reduces pain and improves function in patients with OA of the knee,[6-8] and these beneficial effects are observed in exercise interventions including strength or endurance training.[9-14] However, knowledge of the mechanisms responsible for the beneficial effects of physical training is limited. Specifically, information on the effect of strength training on muscle strength, hypertrophy, and morphology in patients with knee OA is scarce.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used by patients with OA to reduce pain and thereby maintain the ability to perform daily activities. However, in young, healthy individuals, there is accumulating evidence for a negative effect of NSAIDs on skeletal muscle adaptation to physical training.[15-21] NSAIDs are reported to attenuate the increase in muscle protein synthesis in young men after an acute bout of resistance exercise, probably by inhibiting cyclooxygenase activity.[15-17] Additionally, muscle satellite cell activity, which facilitates muscle hypertrophy, is negatively regulated by NSAIDs after an acute bout of resistance exercise[18] or endurance exercise in humans.[19] In rats, NSAIDs have been reported to severely blunt skeletal muscle hypertrophy after a period of

List of Abbreviations

AE	adverse event
CI	confidence interval
CRP	C-reactive protein
CSA	cross-sectional area
KinCom	Kinetics Communicator
KOOS	Knee Injury and Osteoarthritis Outcome Score
MD	medical doctor
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
RM	repetition maximum
SEM	standard error of the mean
VAS	visual analog scale

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muscle overload.[20,21] Consequently, we hypothesized that NSAIDs would inhibit an exercise-induced increase in satellite cells and muscle protein synthesis, and thereby counteract the beneficial muscle adaptations to strength training, in the treatment of patients with OA.

Many patients with OA are treated with glucosamine, and some studies show a beneficial effect of glucosamine sulfate on cartilage and pain.[22-24] However, its effect on OA symptoms and cartilage remains controversial.[25] From a clinical viewpoint, it is important to investigate whether a potentially beneficial effect of glucosamine on joint cartilage can act synergistically with exercise and thereby improve the effects of training.

The primary purpose of the present study was to investigate the differential effects on skeletal muscle strength and muscle mass of a 12-week strength-training program combined with glucosamine, ibuprofen (NSAID), or placebo administration in elderly patients with knee OA. The secondary purpose was to investigate the effect on function (gait speed, chair stand, stair-climbing time, Knee Injury and Osteoarthritis Outcome Score [KOOS] questionnaire), power, pain (visual analog scale [VAS]), satellite cell number, and blood markers (C-reactive protein [CRP] and cholesterol).

METHODS

Study Design

The study was designed as a double-blinded, placebo-controlled, randomized intervention study in which individuals with knee OA performed 12 weeks of strength training. The patients were randomly assigned to treatment with placebo, ibuprofen, or glucosamine in combination with training. Staff personnel not involved in the project randomly assigned patients to the 3 groups using a random number table and prepared the medication for each patient. Study personnel and participants were blinded to treatment assignment, and all analyses were performed blinded to the treatment allocation, subject, and time.

All test measurements were performed before and after the 12-week strength-training period. The patients were familiarized with strength testing and functional testing procedures at least 2 weeks before the pretest-trial.

Participants

The calculations of the required patient number in each group were primarily based on our previous investigation of changes in a serum marker for cartilage turnover (ie, cartilage oligomeric matrix protein) performed on the same group of patients with OA.[26] To detect changes in levels of serum cartilage oligomeric matrix protein of 10% or more at a significance level of .05 with a power of 0.8, and taking into account the interindividual and intraindividual variation as well as variation in the methods for several of the determined parameters in the present study, approximately 10 individuals were required in each group. When power calculations were carried out for the number of patients required to detect an intervention effect on the primary outcome measures of muscle strength and muscle mass, the number of individuals needed was 8. As we determined several parameters in this study, we chose to enroll a number of subjects that even with some dropout would ensure a sufficient number to detect significant changes in all parameters studied. We have not calculated the power for direct differences in the responses between groups because we did not feel we had sufficient previous data for such differences to perform power analysis of this in a qualified and meaningful way.

A total of 36 patients (20 women, 16 men) were recruited in the period January 2005 to January 2006 in Copenhagen (Denmark) via newspaper advertisement. The patients were prescreened via telephone or face-to-face interview. Inclusion criteria were age 50 to 70 years, and bilateral tibiofemoral OA of the knees based on the American College of Rheumatology clinical[27] and radiographic classification criteria with a Kellgren and Lawrence score of 1 to 4.

Frontal anterior-posterior radiographs of both knees were obtained with the patient standing. An experienced radiologist medical doctor (MD) classified each knee for severity of OA using the Kellgren and Lawrence grading system.[28]

On inclusion, an MD examined the patients and established a medical record. Exclusion criteria were cardiovascular disease, active cancer, diabetes, kidney or liver diseases, other rheumatologic diseases, excess alcohol intake (>21 drinks per week for men, >14 for women), severe obesity (body mass index, >35 kg/m^2), knee injury or operation, planned knee joint replacement, previous gastric ulcer, allergy to ibuprofen or glucosamine, and regular training (greater than once weekly). Normal kidney and liver function was verified by analyses of serum creatinine and alkaline phosphatase levels. Furthermore, all patients were negative for rheumatoid factor, and their serum uric acid concentration was in a normal range. On inclusion, patients subjectively scored their average level of daily activity on a VAS from 0 to 10 (0 indicates total inactivity and 10 maximal activity) to estimate their amount of normal physical activity.

All patients provided written informed consent to participate in the study. The experimental protocol was in compliance with the Helsinki Declaration and was approved by the local Ethical Committee for Copenhagen and Frederiksberg Communities (KF 01-189/04) and registered as ClinicalTrials.gov identifier: NCT00833157.

Supplementation

Four patients from each group were previously treated with NSAIDs. Seven patients from the glucosamine group and 5 from both the ibuprofen and placebo groups had previously taken glucosamine. They were instructed to stop the intake a minimum of 1 month before the study began.

Patients were randomly assigned to 1 of 3 medication groups. They were administered glucosamine (n=12), ibuprofen (n=12), or placebo (n=12). Placebo tablets were identical to the glucosamine and the ibuprofen tablets. The administration of pills to all groups started 4 weeks before initiation of training, but treatment with the active NSAID began 1 week before commencement of the study. This was because glucosamine works slowly, taking a few weeks to become effective, and optimally should be given 4 weeks before an assessment is made,[29] whereas ibuprofen works quickly, within hours.[30]

Patients in the glucosamine group were given glucosamine sulfate tablets of 500mg 3 times daily, whereas patients in the ibuprofen group were given tablets of 600mg of ibuprofen twice daily. The treatment was blinded to the patients, so that all patients were supplied the same amount of tablets (5 daily) with a similar appearance. To check compliance, ibuprofen levels in the blood were traced during the training period. Furthermore, to ensure compliance, the patients returned the empty packages every week to a laboratory technician not involved in the study. Additionally, to ensure normal liver and kidney function, blood samples were analyzed for creatinine, CRP, alkaline phosphatase, and total cholesterol before, during, and after the training period. Patients were excluded from the study if these blood parameters were negatively affected or if the patients experienced any other severe side effects from the