
The Journal of Rheumatology

Effect of a Cetylated Fatty Acid Topical Cream on Functional Mobility and Quality of Life of Patients with Osteoarthritis

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ABSTRACT.

Objective. To examine the effect of a topical cream consisting of cetylated fatty acids on functional performance in patients diagnosed with osteoarthritis (OA) of one or both knees.

Methods. Forty patients diagnosed with knee OA were randomly assigned to one of 2 topical treatment groups: (1) cetylated fatty acid (CFA) (n = 20; age 62.7 ± 11.7 yrs); or (2) placebo group (n = 20; age 64.6 ± 10.5 yrs). Patients were tested on 3 occasions: (1) baseline (T1), (2) 30 min after initial treatment (T2), and (3) after 30-day treatment of cream application twice per day (T3). Assessments included knee range of motion (ROM), timed "up-and-go" from a chair and stair climbing, medial step-down test, and the unilateral anterior reach.

Results. For stair climbing ability and the up-and-go test, significant decreases in time were observed at T2 and T3 compared to T1 in the CFA group only. These differences were significant between groups. Supine ROM of the knees increased at T2 and T3 in CFA group, whereas no difference was observed in the placebo group. For the medial step-down test, significant improvement was observed at T2 and T3 compared to T1 in CFA group. For the unilateral anterior reach, significant improvement was observed for both legs in CFA group and in only the left leg in the placebo group. However, the improvements observed in CFA group were significantly greater than placebo group for both legs.

Conclusion. Use of a CFA topical cream is an effective treatment for improving knee

unilateral balance. (J Rheumatol 2004;31:767-74)

Key Indexing Terms:

FATTY ACIDS
OSTEOARTHRITIS
PHYSICAL PERFORMANCE
QUALITY OF LIFE

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Supported in part by a grant from Imagenetix, Inc, San Diego, CA. Dr. Hesslink is a research consultant for Imagenetix, Inc.

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Submitted April 11, 2003; revision accepted August 5, 2003.

Osteoarthritis (OA) is a progressive, degenerative joint disease estimated to affect more than 21 million individuals in the United States[1]. The Arthritis Foundation reports that arthritis is the leading disability of Americans, resulting in over 39 million medical visits per year and US$65 billion in medical expenses and lost wages[2]. The incidence of OA increases with age, and other factors such as fractures involving joint surfaces, joint trauma, ligament tears, meniscal injuries, muscle weakness, and obesity have been linked to OA[3]. OA is characterized by enzymatic and mechanical breakdown of the extracellular matrix, leading to degeneration of articular cartilage[4]. The most common symptoms are pain and stiffness, with an associated reduction in joint range of motion (ROM). Accompanying pain and stiffness are limitations to normal activities of daily living such as getting up from a chair, walking, balance (e.g., greater postural sway), and using stairs[5,6]. In response to pain and stiffness, patients with OA tend to reduce activity, which further induces muscle atrophy and poses greater limitations to performance of activities of daily living. It has been shown that quadriceps strength, joint pain, perceptions of functional ability, and body weight can predict between 39% and 56% of the variance in time to perform various functional tasks[7]. Thus, an intervention that targets pain reduction is necessary in order to improve the quality of life of patients with OA.

Considering the increasing incidence of OA in the elderly population, pain-reducing medications such as acetaminophen, nonsteroidal antiinflammatory drugs (NSAID), and COX-2 inhibitors have been common treatments. However, prolonged intake of NSAID increases the risk of gastrointestinal side effects and renal toxicity, and may inhibit synthesis of cartilage matrix[8-10]. There is a need for alternative products that benefit patients with OA without harmful side effects. Recent investigations have examined treatment with thermal water and hyaluronate sodium and have shown benefits for pain relief and performance enhancement[11,12]. Epidemiological and clinical research indicates that individuals with rheumatoid arthritis (RA) benefit from dietary eicosapentaenoic acid and docosahexaenoic acid (i.e., omega-3 polyunsaturated fatty acids) supplementation[13-15]. In addition, cetylated monounsaturated fatty acids have been shown to provide protection against arthritis in rats[16] and increased knee ROM and reduced pain in patients with OA[17]. However, the effects of topical cetylated fatty acid (CFA) treatment on various activities of daily living (ascending/descending stairs, walking, balance, rising from a chair) remain unknown. We investigated the effect of using a topical cream consisting of a blend of CFA on functional performance and quality of life in patients with OA. We hypothesized that use of a topical CFA cream would result in improved physical function in patients with OA.

MATERIALS AND METHODS

Patients diagnosed with OA by a physician were randomly assigned to one of 2 topical treatment groups in a double-blind manner, receiving either (1) a cream consisting of a blend of CFA; or (2) a placebo cream. To examine any possible immediate effects of treatment, each patient reported to the laboratory and applied a treatment cream to both knees according to the instructions of a primary investigator. After 30 min, each patient was tested for functional performance. This testing session marked the beginning of a 30-day treatment period in which patients applied a cream twice per day every day. Following the 30-day experimental period, each patient returned to the laboratory for post-study functional performance testing. This study design enabled us to examine any potential acute effects of the topical treatment cream and the chronic effects of using this treatment for 30 days. The testing protocols consisted of assessments for knee ROM, postural stability, balance, and ability to rise from a chair, walk, and ascend/descend stairs[27].

All patients selected for study were recruited in conjunction with local physicians from the greater Hartford and Storrs, Connecticut, areas. Each participant was informed of the benefits and risks of the investigation and subsequently signed an approved consent form in accord with the guidelines of the university's Institutional Review Board for use of human subjects. Knee OA was diagnosed using American College of Rheumatology guidelines[18] by the treating physicians, and patients were excluded if they (1) had OA of the hip or ankle, (2) had inflammatory or autoimmune arthritis, (3) were taking steroidal or immune-suppressive agents, and (4) had other serious health problems or could not perform the functional assessments. Patient demographic data are presented in Table 1. No differences were observed between groups in height, body mass, age, or OA history.

To ensure no baseline differences between treatment groups, patients were matched for

either a CFA topical treatment group or a placebo treatment group. Forty-three men and women were originally screened by a physician and began the study. Out of the 43 patients, data for 3 patients were excluded due to non-study related medical complications. Thus, 40 patients completed the study (n = 20 per group; each matched group composed of 17 women and 3 men).

Functional mobility measures. Patients were assessed for functional performance on 3 occasions: during the baseline testing period (T1), 30 min after the initial topical cream application (T2), and after a 30-day experimental period (T3). The selection of assessments and the sequence performed was (1) the timed up-and-go, (2) stair climbing test, (3) unilateral anterior reach, and (4) the medial step-down test. All tests were administered at T1, T2, and T3, with the exception of the unilateral anterior reach, which was administered at T1 and T3 only. The rationale for using this sequence for all testing sessions was to ensure maximal effort by the patient as each test was progressively more difficult and the medial step-down test tended to cause the highest degree of knee pain, thus performing this assessment last in the sequence was most appropriate. All patients participated in 2 familiarization sessions prior to starting the study. All tests were administered by the same investigator to ensure standardization of procedure, and test-retest intraclass correlations producing reliabilities for all the tests ranged from Rs = 0.95 to 0.99.

Timed up-and-go. The timed up-and-go test was performed using standard procedures[19]. The patient sat in a standard armchair. On the verbal signal "go" each patient ascended from the chair, walked until he/she crossed a tape marker located 3 m away, turned around, walked back to the chair, and sat down. Three to 5 trials were performed and the best time was recorded for analysis.

Stair climbing test. Each patient ascended and descended a flight of eleven 13.5 cm steps as quickly as possible. For each trial the total stair time (time to completely ascend and descend the stairs), ascending time (time from the starting point until both feet reached the platform atop the 11th step), and descending time (time from the initial movement of descent until both feet reached the finish point) were recorded. Three to 5 trials were performed and the best times were recorded for analyses. During each trial, patients were allowed to use the handrails and 2 members of the research staff ascended/descended the stairs with the patient to assure maximal safety.

Unilateral anterior reach. This assessment began with the patient's feet oriented with a marker located perpendicular to a tape measure. With hands positioned on the hips, each patient extended a leg out as far as possible (while balancing on the opposite leg), keeping the front foot close to the floor without touching. This induced flexion of the back leg and required a higher degree of muscle strength and balance to perform. A research assistant recorded the displacement attained during each trial. Three to 4 trials were performed for each leg and the trial resulting in the largest displacement was recorded for analysis.

Medial step-down test. The test began with patients standing with both hands on the hips on a 11.4 cm step. Upon the verbal "go" signal, each patient stepped down medially until the heel of the front foot lightly touched the floor and then returned to starting position;

essentially the patient is stepping and touching with one leg while the opposing leg and joint structure bends and supports the movement of the other to floor level. One trial was performed per leg with each patient volitionally performing as many repetitions as possible. The test was terminated when pain was too great or the patient was too fatigued to continue. Any repetition not performed properly was discarded. Verbal encouragement was used to increase performance and 2 spotters were located laterally to the patient for safety.

Clinical assessment. Patients were assessed on basic clinical range of motion of the knees at T1, T2, and T3. For knee ROM, patients were asked to lie supine with both legs fully extended. Patients were then asked to flex each knee as far as possible until discomfort. The joint angle was measured in both the supine extended and flexed positions using a standard goniometer. The same investigator performed all measurements, which yielded test-retest reliabilities of 0.99 for both positions.

Topical cream and application. The topical cream used was a proprietary compound (Celadrin^{TM}, Imagenetix, Inc., San Diego, CA, USA) that consisted of a blend of cetylated fatty acids (cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl palmitate, and cetyl oleate), PEG-100, stearate, benzyl alcohol, lecithin, carbomer, potassium hydroxide, tocopheryl acetate, and olive oil. The placebo cream contained everything but the CFA base material. The topical cream was given to patients in coded tubes so neither the research team involved in testing nor the patient knew which cream was administered.

Patients were instructed to apply a standardized amount of cream to both knees. Cream was applied to the anterior, posterior, and lateral aspects of both knees over a 10–12 cm area twice per day (at a standardized morning and evening time point following a shower) for 30 days. Daily logs were completed to assure proper treatment. Compliance in both CFA and placebo groups was 100% as no patient missed a scheduled topical cream application time.

Nutrition intervention and activity modification. Each patient was instructed to maintain his/her current food/beverage intake throughout the 30-day experimental period as monitored by a registered dietician. This was to ensure patients did not gain or lose weight during the study, which could have affected performance on many of the assessments. Diet counseling and 3-day food records were completed prior to initiation of the study and each patient was instructed on how to maintain current dietary practices. As a result, body mass did not change in either group: CFA group: pre-testing = 85.6 ± 20.6 kg, post-testing = 85.7 ± 20.5 kg; placebo group: pre-testing = 84.6 ± 21.8 kg, post-testing = 84.5 ± 21.7 kg, and no baseline (T1) differences were observed as patients were matched prior to random assignment. In addition, patients were taking no additional arthritis medications during the study but were instructed to maintain their current life-sustaining medication routine (i.e., medications for blood pressure and cholesterol) throughout the study. Patients were screened and recruited between therapeutic treatments for at least 2 months and were not currently taking OA related medications or treatments. Patients were instructed not to begin taking any medications/supplements or start any new OA treatment regimens over the course of the study. Each patient was instructed to maintain his/her current activity level

initiate a new exercise program during the study. In addition, patients were not permitted to practice the performance tests used in the study to prevent any training effects.

Statistical analyses. Statistical evaluation of all data was accomplished using a 2×3 analysis of variance with repeated measures. Subsequent pairwise differences were determined using a Tukey post-hoc test when appropriate. Statistical power for the various dependent variables was determined to be 0.80–0.85 for the sample size used at the 0.05 alpha level (nQuery Advisor® software; Statistical Solutions, Saugus, MA, USA). Significance was set at $p \leq 0.05$.

RESULTS

☐ ***Table 1.*** **Patient demographic data. No significant differences between groups were observed ($p \geq 0.60$).**

The results of the timed up-and-go test are presented in Figure 1. Significant main effects [$F(2,37) = 16.98$, $p < 0.001$] and interactions [$F(2,37) = 4.49$, $p < 0.018$] were observed; at T2, both treatments resulted in significant reductions in time. The magnitude of improvement was significantly greater in the CFA group. At T3, both treatments resulted in a significant decrease in time compared to T1, with the magnitude of improvement significantly greater in CFA group. However, only the CFA group significantly improved between T2 and T3.

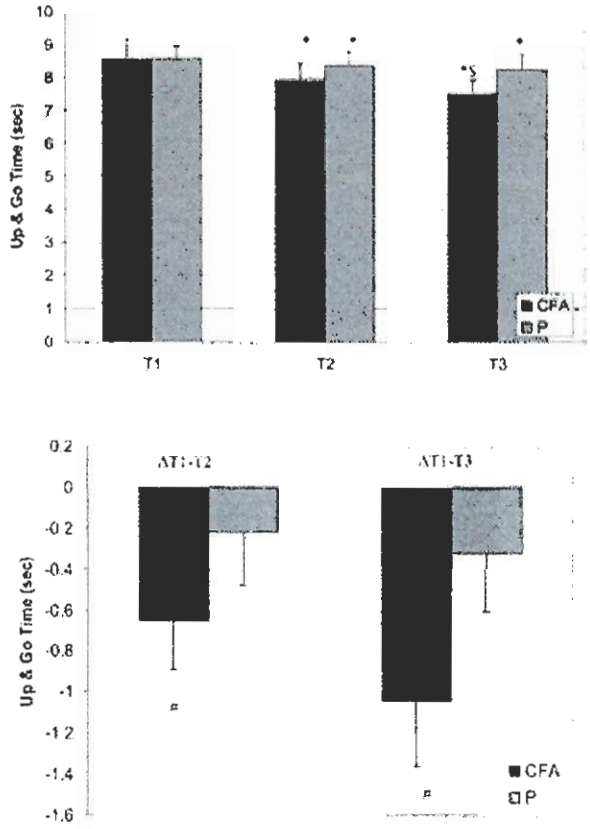

Figure 1. The timed up-and-go assessment in patients using the CFA topical cream or placebo (P). Top panel: the main effects at T1, T2, and T3. Bottom panel: group interactions in differences from T1 to T2 and from T1 to T3. Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1. #: $p < 0.05$ between groups. $: $p < 0.05$ from corresponding time point T2.

The results of the timed stair climbing test are presented in Figures 2–4. For total stair climbing time, significant main effects [$F(2,37) = 14.18$, $p < 0.001$] and interactions [$F(2,37 = 11.94$, $p < 0.001$] were observed. At T2, a significant reduction in time was observed in CFA group only. At T3, significant reductions in time were observed in CFA group compared to T1 and T2. The improvements at T2 and T3 compared to T1 were significantly greater in CFA group than placebo group. For ascending stair climbing time, significant main effects [$F(2,37) = 14.40$, $p < 0.001$] and interactions [$F(2,37) = 13.00$, $p < 0.001$] were observed. At T2, a significant reduction in time was observed in CFA group only. At T3, significant reductions in time were observed in CFA group compared to T1 and T2. The improvements at T2 and T3 compared to T1 were significantly greater in CFA group than placebo group. For descending stair climbing time, significant main effects [$F(2,37) = 6.93$, $p < 0.003$] and interactions [$F(2,37) = 6.32$, $p < 0.004$] were observed. At T2, a significant reduction in time was observed in CFA group only. At T3, significant reductions in time were observed in CFA group compared to T1 and T2. The improvements at T2 and T3 compared to T1 were significantly greater in CFA group than placebo group. No differences

were observed in placebo group at any time point.

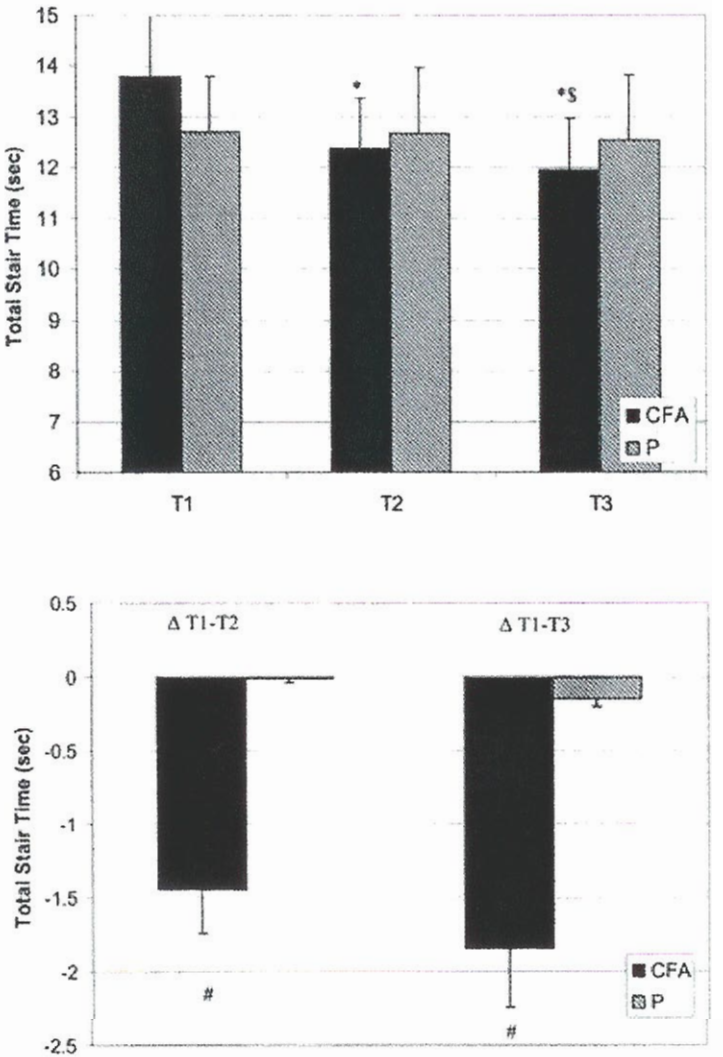

Figure 2. Timed stair climbing assessment in patients using CFA topical cream or placebo (P). Top panel: the main effects at T1, T2, and T3. Bottom panel: group interactions in differences from T1 to T2 and from T1 to T3. Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1. #: $p < 0.05$ between groups. $: $p < 0.05$ from corresponding time point T2.

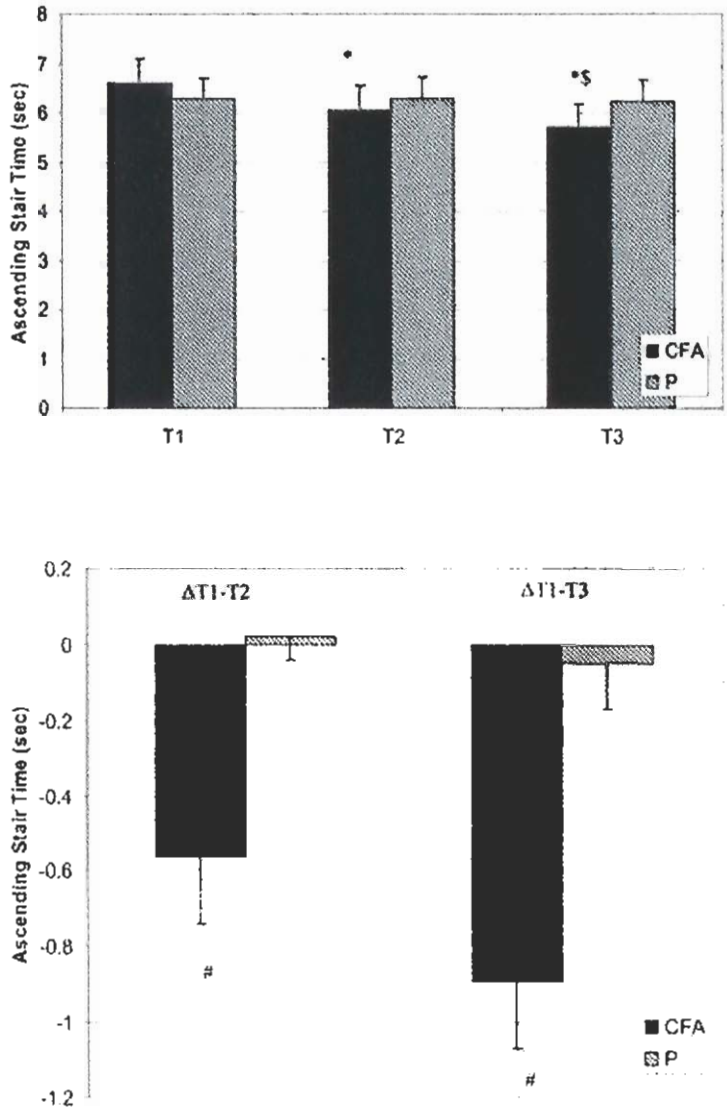

Figure 3. Time to ascend stairs in patients using CFA topical cream or placebo (P). Top panel: the main effects at T1, T2, and T3. Bottom panel: group interactions in differences from T1 to T2 and from T1 to T3. Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1. #: $p < 0.05$ between groups. $: $p < 0.05$ from corresponding time point T2.

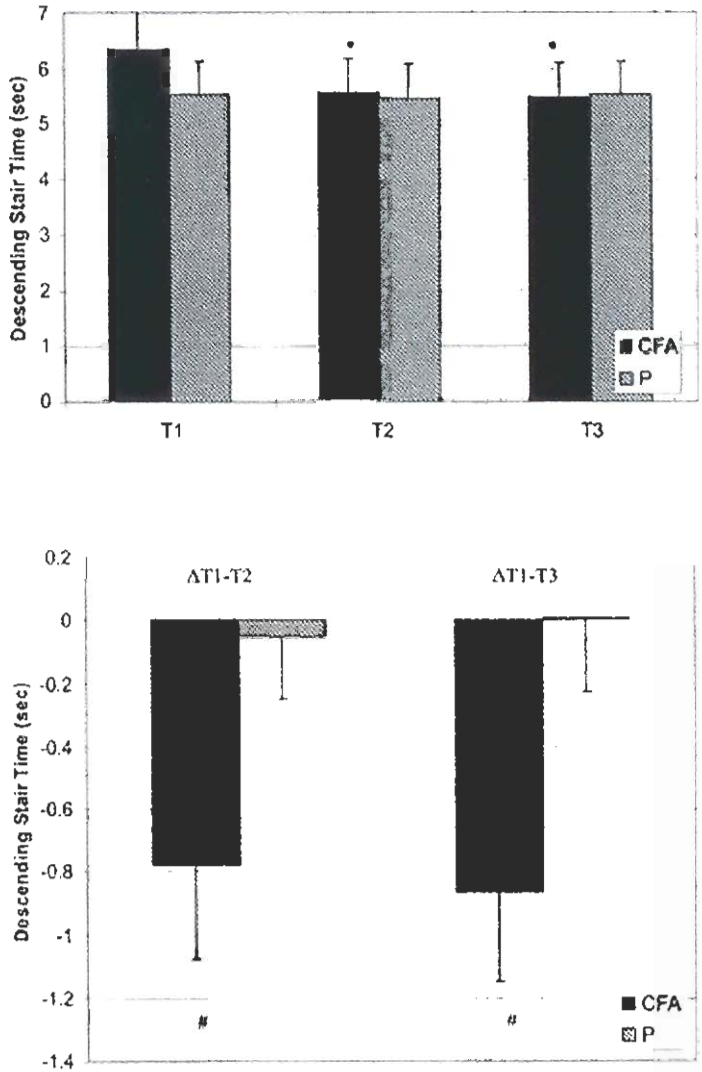

Figure 4. Time to descend stairs in patients using CFA topical cream or placebo (P). Top panel: the main effects at T1, T2, and T3. Bottom panel: group interactions in differences from T1 to T2 and from T1 to T3. Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1. #: $p < 0.05$ between groups.

Results of the unilateral anterior reach test are presented in Figure 5. For the right leg, significant main effects [$F(2,37) = 23.50$, $p < 0.001$] and interactions [$F(2,37 = 12.19$, $p = 0.001$] were observed. At T3, a significant increase (5.2 cm) was observed in CFA group and this increase was significantly greater than placebo group. For the left leg, significant main effects [$F(2,37) = 17.49$, $p < 0.001$] and interactions [$F(2,37) = 4.08$, $p < 0.05$] were observed. Both CFA group and placebo group increased at T3. However, the increase in CFA group (4.3 cm) was significantly greater than placebo group.

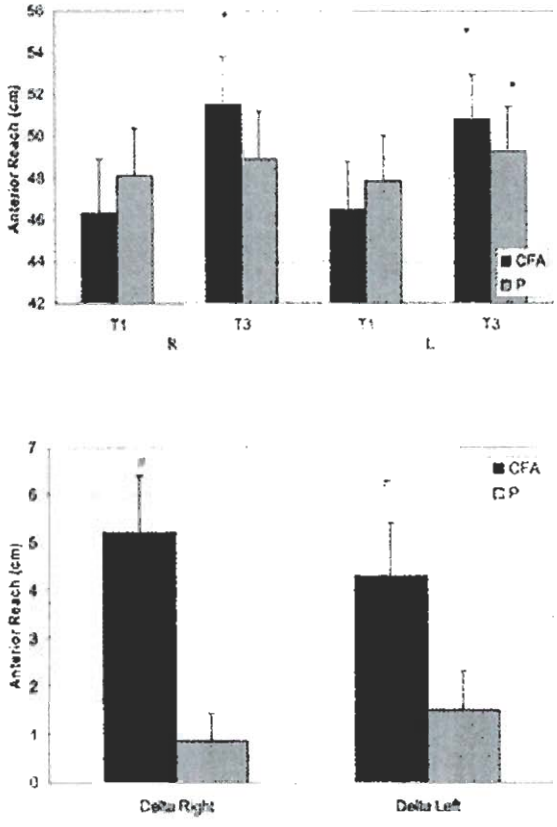

Figure 5. The unilateral anterior reach assessment in patients using CFA topical cream or placebo (P). Top panel: the main effects at T1 and T3. Bottom panel: group interactions in differences from T1 to T3. Data are means ± SE. R: right leg; L: left leg; T1: baseline; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1. #: $p < 0.05$ between groups.

Results of the medial step-down test are presented in Figure 6. For the right leg, significant main effects [$F(2,37) = 12.36$, $p < 0.001$] and a trend for an interaction [$F(2,37 = 2.68$, $p = 0.08$] were observed. At T2, significant increases were observed in both groups. However, at T3 only CFA group demonstrated an increase compared to T1 and T2, and the delta change between T1 and T3 tended to be greater in CFA group than placebo group. For the left leg, only a significant main effect [$F(2,37) = 5.36$, $p < 0.009$] was observed. The number of repetitions performed at T2 and T3 was significantly greater than T1 in CFA group whereas no significant difference was observed in placebo group.

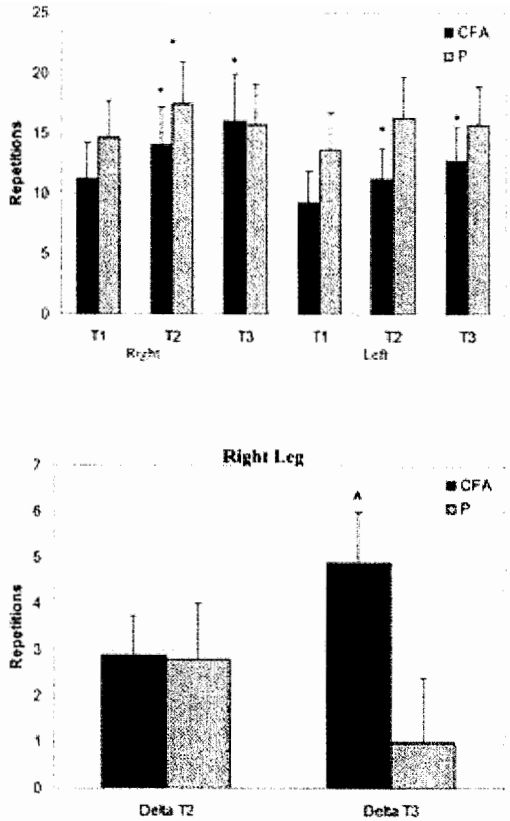

Figure 6. The medial step-down assessment in patients using CFA topical cream or placebo (P). Top panel: the main effects at T1, T2, and T3. Bottom panel: group interactions in differences from T1 to T2 and from T1 to T3 for the right leg only (no differences were observed for the left leg). Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1; ∧: $p = 0.08$ between groups.

Results of the knee ROM assessments are presented in Figure 7. Supine flexed position: for the right leg, a significant main effect [$F(2,37) = 7.89$, $p < 0.001$] was observed with no significant interaction [$F(2,37 = 2.50$, $p = 0.096$]. At T2 and T3, significant increases were observed compared to T1 in CFA group only. For the left leg, a significant main effect [$F(2,37) = 8.31$, $p < 0.001$] and an interaction [$F(2,37 = 3.27$, $p < 0.05$] were observed. At T2 and T3, significant increases were observed compared to T1 in CFA group only. The knee ROM was significantly greater in CFA group than placebo group at T2 and T3. Supine flexed knee ROM did not change in placebo group. Supine extended position: for the right leg, no significant difference was observed [main effect: $F(2,37) = 1.85$, $p = 0.17$; interaction: $F(2,37) = 1.36$. $p = 0.27$]. For the left leg, a significant main effect [$F(2,37) = 3.38$, $p = 0.045$] was observed. At T3, a significant decrease was observed compared to T1 in CFA group only. No difference in the ability to extend the leg in a supine position was observed in placebo group.

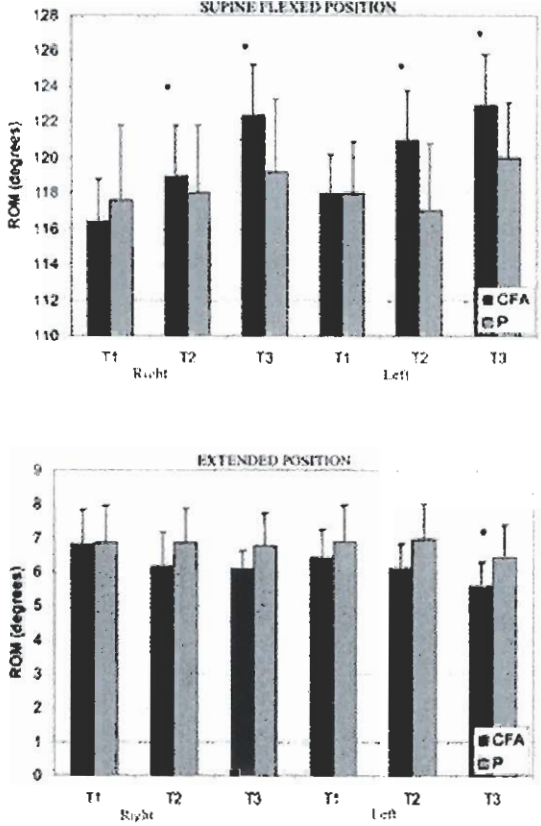

Figure 7. Knee ROM in patients using CFA topical cream or placebo (P). Top panel: supine flexed knee ROM. Bottom panel: supine extended knee ROM. Data are means ± SE. T1: baseline; T2: acute response to initial cream application; T3: post 30-day treatment period. *$p < 0.05$ from corresponding time point T1.

DISCUSSION

Our findings indicate a topical cream consisting of a blend of CFA is effective for (1) improving knee ROM; (2) improving ability to climb stairs, rise from a chair, and walk; and (3) improving balance, strength, and endurance in patients with knee OA.

The process of inflammation in OA involves the release of proinflammatory cytokines (e.g., interleukin 1ß and tumor necrosis factor-α). Fatty acids, especially n-6 fatty acids, have been proposed to reduce chronic inflammation in patients with RA by reducing leukotriene B_4 from stimulated neutrophils and of interleukin 1 monocytes[15,20]. In addition, other suggested mechanisms for the antiinflammatory response observed with fatty acid treatment are reduced expression and activity of proteoglycan degrading enzymes and cytokines, suppression of leukocyte function, changes in adhesion molecule expression and apoptosis triggering, and alterations in signal transduction and membrane fluidity[15,21,22]. Cetylated monounsaturated fatty acids have been shown to provide protection against arthritis in rats[16]. In addition, a study has shown that a CFA complex increased knee ROM and reduced pain in patients with OA[17]. Although the mechanisms remain to be elucidated, the results of

our investigation support previous research and indicate that a topically-applied CFA complex improves physical function, performance, and the quality of life in patients with knee OA.

Functional performance is limited in patients with knee OA[23]. Patients with knee OA have been shown to walk on a flat surface and ascend and descend stairs with significantly less velocity than healthy individuals[23]. In addition, peak knee extensor moments during normal gait are reduced in patients with OA, demonstrating a compensation for knee pain[23]. Several factors may explain the reduction in physical performance capacity. It has been shown that quadriceps strength, joint pain, perception of functional ability, and body weight combined may explain 39–56% of the variance in time to perform common functional tasks (e.g., ascending/descending stairs) in patients with knee OA[7]. Standing balance (e.g., postural sway) has been shown to be limited in patients with OA[6], partially due to strength reductions[24-26]. Muscle activation is also significantly impaired in patients with knee OA[5]. In addition, inactivity associated with OA pain results in further atrophy and loss of muscle strength, power, endurance, and potential weight gain, which further exacerbates the condition and results in decrements in quality of life. Perhaps the most substantial improvement observed in this study was stair climbing ability. Treatment with a CFA topical cream was very effective for improving stair climbing ability, whereas the placebo group showed no change. The most remarkable finding was that stair climbing ability improved immediately after 30 min of initial treatment. These data suggest that the rapid improvement observed in ascending/ descending stair times may have been due to immediate pain relief and reduced stiffness. In addition, further improvement was observed after 30 days of treatment (T3), revealing a chronic effect of CFA topical treatment. Considering that many patients with knee OA have difficulty ascending and/or descending stairs and tend to minimize stair climbing, our data show a beneficial effect of topically-applied CFA for improving functional performance.

The ability to rise from a chair and walk is another functional performance task that is limited in patients with knee OA[5]. Recently, McGibbon and Krebs[28] reported that patients with arthritis had lower walking speed, stride length, reduced ankle and knee power, and abnormal knee kinematics (which were exacerbated by higher speeds of walking) compared to matched controls. Thus, compensation for pain appears to negatively alter walking mechanics in patients with arthritis. Our results indicated significant enhancement of performance with topical CFA treatment. Immediate improvements were observed at T2 and further improvement was observed following 30 days of treatment. Interestingly, a small improvement was also observed mostly at T2 in the placebo group. This may have been due to the acute effects of massage[29]. During cream application, patients were instructed to apply the cream around the circumference of the knees but to emphasize the areas of greatest pain, thereby massaging this area. Considering that reduction in pain may have occurred and that the up-and-go was the first performance test following topical cream application, it is possible that the small improvement may have been related to acute effects of massage and subsequent pain relief. We have no data regarding the absorption of the CFA cream through the skin and into the joint, but such studies should be a topic of further investigation of the mediating mechanisms. Nevertheless, the improvements with CFA were significantly greater than placebo, showing a beneficial effect of topical CFA application

for improving timed up-and-go performance in patients with knee OA.

The unilateral anterior reach and medial step-down tests were included because of their reliance on balance, strength, and endurance during performance. Studies have shown a relationship between muscle strength and balance[24-26] and both of these are adversely affected by knee pain. Our results indicated that unilateral anterior reach performance was greater in the CFA group for both legs at T3 (this test was not included at T2). These results suggest improvements in balance and strength (i.e., greater ability to eccentrically flex the support leg while maintaining body weight stability and consequently extend the front leg a greater distance) possibly resulting from chronic pain relief over the 30-day experimental period. Similar results were obtained for the medial step-down test. Both study groups improved at T2 but only the CFA group improved at T3. The improvements observed at T2 (and not T3) in the placebo group suggest that acute massage may have contributed, in part, to the enhanced performance. Interestingly, the delta change from T1 to T3 was greater in the CFA group for the right leg only. From our data, the majority of the patients reported greater pain and stiffness in the right knee. Therefore, these data have greater influence, considering that the right knee was most affected by OA in our sample.

Topical treatment with cetylated fatty acids significantly increased physical performance (e.g., balance, stair climbing ability, ability to rise from a chair, and walking) in patients with knee OA. A unique finding was an immediate effect of this treatment 30 min after initial cream application. The results of this study provide support for the use of cetylated fatty acids as part of a pain relief treatment in patients with knee OA.

ACKNOWLEDGMENT

We thank our patients who made this project possible. We also thank our research assistants, our network of referring physicians, and clinical assistants for their support.

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