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Cetylated Fatty Acids Improve Knee Function in Patients with Osteoarthritis

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ABSTRACT.

Objective. To determine the benefit of cetylated fatty acids (CFA) on knee range of motion and function in patients with osteoarthritis (OA).

Methods. Sixty-four patients with chronic knee OA were evaluated at baseline and at 30 and 68 days after consuming either placebo (vegetable oil; n = 31) or CFA (Celadrin™; n = 33). Evaluations included physician assessment, knee range of motion with goniometry, and the Lequesne Algofunctional Index (LAI).

Results. After 68 days, patients treated with CFA exhibited significant ($p < 0.001$) increase in knee flexion (10.1°) compared to patients given placebo (1.1°). Neither group reported improvement in knee extension. Patient responses to the LAI indicated a significant ($p < 0.001$) shift towards functional improvement for the CFA group (-5.4 points) after 68 days compared to a modest improvement in the placebo group (-2.1 points).

Conclusion. Compared to placebo, CFA provides an improvement in knee range of motion and overall function in patients with OA of the knee. CFA may be an alternative to the use of nonsteroidal antiinflammatory drugs for the treatment of OA.

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Dietary fatty acid composition is important for the prevention of chronic disease[1-4]. Results of epidemiological research indicate that individuals consuming diets high in fish oils have a lower incidence of cardiovascular disease[2-4]. It has subsequently been shown that eicosapentaenoic acid (EPA) is the main component of fish oils providing this protective benefit. EPA, an eicosanoid precursor, and docosahexaenoic acid (DHA) are omega-3 polyunsaturated fatty acids[5-7]. Epidemiological and clinical research indicates that individuals with rheumatoid arthritis (RA) also benefit from dietary EPA and DHA supplementation[8-11], although outcomes have been variable. Recently, it was shown that a cetylated monounsaturated fatty acid (e.g., myristoleic acid) conferred protection against adjuvant-induced arthritis in rats[12]. However, the mechanism of action was not established. A

recent study suggested that myristoleic acid may act by inhibition of 5-lipoxygenase[13], a potent mediator of inflammation[14].

The incidence of osteoarthritis (OA) is rising among the elderly[15]. Nonsteroidal antiinflammatory drugs (NSAID) including COX-2 inhibitors are commonly used treatments; however, longterm use of these agents may lead to significant adverse events[16-21]. There is a need for alternative products that benefit patients with OA without harmful side effects. Recently, several products containing cetyl myristoleate oil have become available. However, well-controlled studies to investigate the efficacy of these products have not been performed. We investigated the clinical benefits of a blend of cetylated monounsaturated fatty acids in a group of patients with OA of the knee. We hypothesized that these patients would experience improvement in knee range of motion and clinical status based on the Lequesne Algofunctional Index (LAI)[22] questionnaire.

MATERIALS AND METHODS

Patients and consent. Two medical clinics were enlisted for recruitment of patients in an OA study approved by the Maiya Hospital IRB in Bangalore, India. Of the 86 patients expressing interest, 66 patients were selected due to their diagnosis of knee OA (placebo: n = 33; CFA: n = 33). Knee OA was diagnosed using American College of Rheumatology guidelines[23] by the treating physician and confirmed by the clinical investigator (MVN).

Study design. Subjects were randomized to study intervention. Subjects and investigators were blinded to treatment assignment. Amber colored soft gel capsules identical in shape and size were used to blind study participants. Patients were asked to consume 6 capsules per day with makeup days allowed for missed dosages. Subjects were asked to consume 3 capsules in the morning and 3 in the evening (total = 408 capsules).

After initial clinical assessment, the patients were asked to maintain their daily dietary and medication routine. Subjects receiving medication for other ailments were asked to maintain their current dosing regimen. In addition, patients currently taking medication for knee OA were asked to continue their medication (Table 1). Patients unable to adhere to this requirement were dropped from the study. The patients returned after 30 days for their second clinical assessment and after 68 days for their final assessment.

Clinical assessment. Patients were assessed on basic measures during 3 visits (baseline, Day 30, and Day 68) to the main clinic. One clinical investigator (MVN) interviewed and evaluated each patient by physical examination. Observations for pain, stiffness, and discomfort were recorded. Patients were asked to lie supine for assessment of knee range of motion, and while lying supine the patient was asked to extend both legs straight. Patients were then asked to flex each knee as far as possible until discomfort. The angle was then measured using a standard goniometer with the measurement rounded in 5° increments (e.g., 72° rounded to 70° and 83.5° rounded to 85°).

Patients were then asked a series of questions. The same staff member met with the patient during each visit. These questions were taken from the LAI, which has been used extensively in European OA studies since 1980. Basically, the LAI includes 3 sections with a total of 10 questions and a total of 24 points (Appendix). The first section addresses pain and discomfort (8 points), the second section addresses walking distance (8 points), and the third section addresses physical function (8 points).

Nutritional intervention. Patients in the placebo group received capsules containing 500 mg of soy lecithin (ADM Company, Decatur, IL, USA). The treatment group received capsules containing 350 mg Celadrin™ (Imagenetix Inc., San Diego, CA, USA), 50 mg soy lecithin, and 75 mg of a standard fish oil blend containing a total omega-3 concentration of 37%, with EPA 17.56% and DHA 12.63% (Arista Industries, Wilton, CT, USA). Celadrin™ is a blend of olive oil (30%) and cetylated fatty acids (cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laurate, cetyl palmitate, cetyl oleate).

Statistical analysis. Demographic and knee flexion data were analyzed using ANOVA with repeated measures (JMP, SAS Inc., Cary, NC, USA). The responses to the LAI questionnaire were analyzed using a one-way analysis of variance assuming continuous data and an ordinal logistic regression, which estimates the cumulative probability of being at or below each individual response level. All statistics were 2 tailed and significance was set at $p < 0.05$.

RESULTS

The variety of medications taken during the trial was similar between groups (Table 1). The 2 groups were similar on baseline measures of age, weight, height, and sex. History of OA was significantly different between the 2 groups ($p < 0.004$) (Table 2). Two patients were dropped from the placebo group due to compliance issues.

Table 1. Summary of patient medications during study period.

Medications	CFA Group (n)	Placebo Group (n)
Aspirin	6	5
Ibuprofen	8	8
Ketoprofen	6	7
Celecoxib	3	0
Nimesulfide	1	6
Diclofenac	3	4
None	6	1

Table 2. Patient demographics (data presented as mean ± standard deviation).

	CFA Group n = 33	Placebo Group n = 31
Age (yrs)	58.1 ± 6.3	55.5 ± 6.8
Weight (kg)	74.8 ± 9.0	78.0 ± 8.1
Height (cm)	163.3 ± 8.5	166.10 ± 8.4
M:F	22:11	17:14
Years of OA*	6.94 ± 1.89	5.54 ± 1.84

* Significant difference ($p < 0.004$).

Physical examination by the clinical investigator revealed minimal improvements in swelling over the course of the study. Fifteen percent of the CFA group experienced reductions in swelling, compared to none of the placebo group. In the CFA group 58% of patients experienced a reduction in pain compared to 32% of patients given placebo. Neither group exhibited changes in morning stiffness.

There was a significant ($p < 0.001$) improvement in knee flexion (Figure 1) for the CFA group at Days 30 and 68, whereas knee extension remained unchanged for both groups. Power analysis from observed changes in knee flexion revealed that a minimum of 12 patients per group would have detected a 3.7° difference between groups with a power of 90% ($\alpha = 0.05$, 2 tailed).

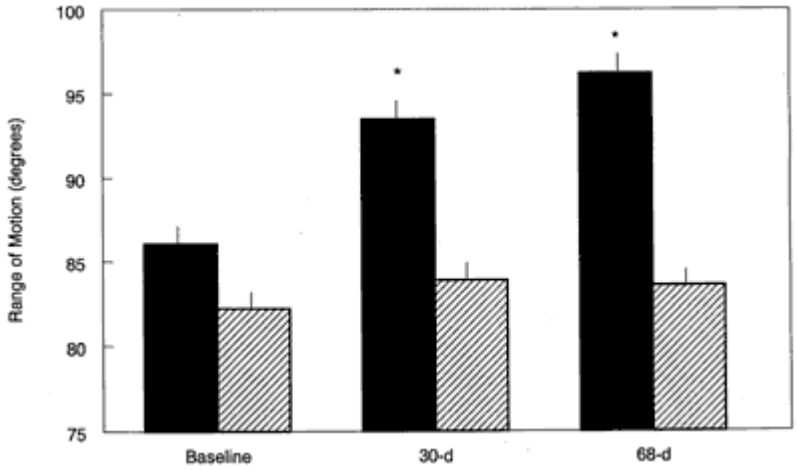

Figure 1. Knee range of motion in patients consuming cetylated fatty acid supplements for 68 days. Data represented as mean ± SE. *Significant difference ($p < 0.001$) compared to placebo.

The LAI categorized both treatment groups as initially having extremely severe OA (LAI > 14). Table 3 shows the average subject response to the LAI. When analyzed as continuous data, all 4 response categories declined significantly ($p < 0.001$ versus baseline) for the CFA group by Day 68. This was not observed in the placebo group. Moreover, treatment interaction was significant for the pain category ($p < 0.049$) but not for distance or activity. The total category suggested an improvement in the CFA group compared to placebo ($p < 0.055$). Power analysis of the observed data at Day 68 revealed a power of 61% ($\alpha = 0.05$, 2 tailed). To achieve 90% power from the observed data, 66 subjects per group would be required.

Table 3. Lequesne Algofunctional Index of knee OA. Each value, mean ± SE, is the average sum of the Lequesne questions for all subjects in each group. The range of averages is in parentheses. The CFA group noted improvement resulting in a lower total response compared to placebo.

	CFA Group			Placebo Group		
	Baseline	Day 30	Day 68	Baseline	Day 30	Day 68
Total	15.6 ± 0.6	10.6 ± 0.7	10.2 ± 0.7*	15.8 ± 0.7	13.7 ± 1.07	13.7 ± 1.07
	(14.4-16.7)	(9.0-12.0)	(8.7-11.8)	(14.3-17.3)	(11.5-15.9)	(11.5-16.0)
Pain	6.0 ± 0.1	4.0 ± 0.3	3.9 ± 0.3**	6.1 ± 0.2	5.1 ± 0.4	5.1 ± 0.4
	(6.0-6.4)	(3.3-4.7)	(3.2-4.6)	(5.6-6.6)	(4.2-6.0)	(4.2-6.0)
Walking	4.7 ± 0.3	3.5 ± 0.3	3.4 ± 0.3	4.9 ± 0.3	4.6 ± 0.4	4.6 ± 0.4
	(4.1-5.4)	(2.9-4.1)	(2.7-4.0)	(4.2-5.6)	(3.8-5.4)	(3.8-5.3)
Activity	4.6 ± 0.2	3.5 ± 0.3	3.1 ± 0.3	4.8 ± 0.2	4.2 ± 0.3	4.2 ± 0.3
	(4.1-5.1)	(2.5-3.7)	(2.5-3.7)	(4.2-5.2)	(3.6-4.8)	(3.5-4.8)

* $p < 0.055$; ** $p < 0.049$ determined by one way analysis of variance with repeated measures.

The LAI was further analyzed for noncontinuous data using ordinal logistic regression. This technique allows for the determination of probability estimates for the observed to predicted responses. The probability estimates

shown in Table 4 reflect the treatment interaction between groups at baseline and Day 68. All questions achieved probability estimates less than 0.05 except when patients responded to the question regarding pain after standing. These data show that, overall, the CFA group tended to produce a greater positive influence on patient perception as noted by their individual responses to each question.

Table 4. Probability estimates for Lequesne Algofunctional Index.

Question*	Variable Estimates**	Standard Error	Probability
Nocturnal	0.987	0.170	< 0.0001
Morning stiffness	0.181	0.160	< 0.0057
Pain after standing	0.591	0.338	> 0.08
While ambulating	0.410	0.148	< 0.0056
Getting up	0.486	0.173	< 0.005
Maximum distance	0.554	0.145	< 0.0001
Upstairs	0.340	0.194	< 0.0388
Downstairs	0.424	0.154	< 0.0057
Able to squat	0.381	0.153	< 0.0128
Walk uneven	0.819	0.204	< 0.0001

* See Appendix for complete Lequesne questions, ** In the ordinal model, data are fitted to the cumulative response probabilities of the logistic distribution function of a linear model using maximum likelihood. Likelihood ratios are provided for the whole model. The above probability estimates test for differences between those subjects receiving CFA and those receiving placebo.

DISCUSSION

Diehl and May[12] reported in 1994 that the cetylated fatty acid, cetyl myristoleic acid, afforded significant protection against adjuvant induced arthritis in rats. Although many products containing cetyl myristoleic acid are now available, research based evidence of their efficacy has been lacking. Our placebo controlled study documents the clinical benefits of a cetylated monounsaturated fatty acid blend for the treatment of patients with OA of the knee. The intervention used in this study consisted of cetylated monounsaturated fatty acids with nominal amounts of fish oil and olive oil used for suspension. CFA treated patients exhibited improvements in knee flexion and function as measured by the LAI.

Epidemiological surveys provided the initial data that highlighted the value of marine fish oils in treatment of chronic diseases[1-7]. Considerable data show the benefits of fish oil for RA but little information exists about treatment of OA. The rationale for fish oil supplementation is that these fatty acids alter the lipid content of membrane phospholipids and reduce the production of the eicosanoids that mediate inflammation. Fish oils also reduce cytokine synthesis and suppress cell activation[7,24]. It is generally recognized that a minimum of 3 g/day of EPA and DHA is required to derive expected benefits[25], although it has been suggested that levels as low as 2.25 g/day of EPA and DHA can manipulate neutrophil fatty acid composition[26]. Since our subjects received only 0.45 g/day fish oil, the fish oil probably had a very minimal role in producing the benefits achieved by our patients.

Monounsaturated fatty acids like olive oil have been shown to inhibit endothelial activation[27,28] and to reduce tissue responsiveness to cytokines[29-31]. In addition, cetylated myristoleic acid confers protection in adjuvant induced arthritis[12]. While the mechanism of action for cetylated myristoleic acid is beyond the scope of this

discussion, a recent study using an extract from the native herb saw palmetto (*Serenoa repens*) was shown to induce cell death in human prostate cells[13]. The main component of this extract appears to be myristoleic acid and the authors speculated that this apoptosis may be due to *de novo* ceramide formation and/or 5-lipoxygenase inhibition. It is this inhibition of 5-lipoxygenase that may explain in part the action of myristoleic acid and its cetylated form in our study. The byproducts of 5-lipoxygenase are potent mediators of inflammation and allergic reactions[14,32]. Indeed, it was suggested as early as 1995[14] that lipoxygenase byproducts may participate in inflammatory processes leading to joint destruction in RA.

The salient feature of our study is that our patients achieved appreciable increases (+10.1°) in knee range of motion that were above the detectable level determined via power analysis. The ability of individuals with knee OA to ambulate is compromised compared to healthy individuals. Walker, *et al*[33] reported that knee flexion in patients with OA (98.6°) was reduced significantly compared to controls (137.5°) during all activities. Comparable knee flexion data for monounsaturated fatty acids and marine fish oils do not exist. However, when compared with traditional medications used for knee OA, the data presented here are equivalent. For example, in an early study investigating the benefit of naproxen and diflunisal, it was shown that patients with OA achieved significant improvement in knee flexion of 7.5° after 12 weeks[34]. Another trial investigated traditional NSAID (e.g., etodolac and piroxicam) in degenerative knee joint disease. Improvements from 6.0° to 7.7° were reported after 6 weeks of treatment[35]. A recent study evaluated aceclofenac and piroxicam in OA patients over a 2 month period[36]. These patients experienced knee flexion improvement of 12.4° and 8.1°, respectively. In addition, these patients experienced a reduction in the LAI. Patients receiving aceclofenac experienced a decrease of 4.6 points whereas patients receiving piroxicam experienced a decrease of 5.0 points. Herrmann, *et al*[37] reported that diclofenac and oxaceprol elicited decreases in the LAI after 21 days (-2.8 and -2.5, respectively).

Patients using the CFA in our study noted a reduction (-5.0) in the overall LAI after 30 days, which remained unchanged after 68 days (-5.4). Analyzed as continuous data, the overall treatment interaction tended to suggest an improvement ($p < 0.055$) compared to the placebo group. However, ordinal logistic regression showed an almost overwhelmingly positive response to LAI with CFA compared to placebo. It is worth noting that power analysis proved conclusive for our knee flexion data but suggested that an increased group sample size would have benefited the LAI data set.

The CFA provided relief even for those individuals also receiving traditional medications (Table 1). These results are even more impressive considering a recently published 5 year study showed only a minimal improvement in LAI (-0.53 points) in patients given intraarticular injections of a glycosaminoglycan peptide complex compared to controls (-1.53 points)[38].

OA is due to a combination of mechanical, biochemical, and genetic factors that contribute to the breakdown of the articular cartilage[39]. Because NSAID including the new COX-2 inhibitors have potentially serious side effects[16-21], more patients are seeking nontraditional treatments. Results of many of these have not been conclusive[40], although more recent data have shown the beneficial use of glucosamine[41]. Our results suggest that cetylated fatty acids are effective in improving the symptoms of OA and therefore should be considered as a viable option for treatment of this condition.

In summary, the use of a cetylated fatty acid complex improved knee range of motion and function in patients with OA of the knee of 5 to 6 years' duration. Further studies are warranted to determine whether these fatty acids alter the 5-lipoxygenase enzyme through either substrate or inhibitory mechanisms and change subsequent leukotriene production.

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APPENDIX

Lequesne Algofunctional Index questions for knee OA. The subject is asked to respond on a 5 point Likert scale (0, 0.5, 1, 1.5, and 2; 0 is without difficulty and 2 is with difficulty or discomfort).

Pain or discomfort

1. During nocturnal bedrest
   - None or insignificant
   - Only on movement or in certain positions
   - With no movement
2. Morning stiffness or regressive pain after rising
   - 1 min or less
   - More than 1 but less than 15 min
   - 15 min or more
3. After standing for 30 min
4. While ambulating
   - None
   - Only after ambulating some distance
   - Early after initial ambulation and increasingly with continued ambulation
   - After initial ambulation, not increasingly
5. While getting up from sitting without help of arms
6. Maximum distance walked (may walk with pain)
   - Unlimited
   - More than 1 km, but limited
   - About 1 km (0.6 mi) in about 15 min
   - From 500 to 900 m in about 8 to 15 min
   - From 300 to 500 m
   - From 100 to 300 m
   - Less than 100 m
   - With one walking stick or crutch
   - With 2 walking sticks or crutches

Activities of daily living

7. Able to climb up a standard flight of stairs
8. Able to climb down a standard flight of stairs
9. Able to squat or bend on the knees
10. Able to walk on uneven ground

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