Am J Transl Res 2022;14(10):7252-7259
www.ajtr.org /ISSN:1943-8141/AJTR0144312

Original Article

Effect of dietary flaxseed oil on the prognosis of acute anterior cruciate ligament rupture: a randomized placebo-controlled trial

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Received May 22, 2022; Accepted August 30, 2022; Epub October 15, 2022; Published October 30, 2022

Abstract: Objective: This study aimed to explore whether dietary flaxseed oil has effects on acute anterior cruciate ligament (ACL) rupture prognosis after surgical reconstruction. Methods: Patients with primary acute ACL rupture diagnosed by magnetic resonance imaging and clinical examination were recruited at Quanzhou First Hospital Affiliated to Fujian Medical University and randomized to either the placebo group or the flaxseed oil group by computer-generated random numbers. Patients in the placebo group took six corn oil capsules daily, while patients in the flaxseed oil group took six flaxseed oil capsules daily. The outcomes were evaluated by specific scales. Results: Compared to the placebo group, the flaxseed oil group showed significantly higher International Knee Documentation Committee (IKDC) score (P = 0.007) and total Knee Injury and Osteoarthritis Outcome Score (KOOS) (P = 0.0003) after two-year administration. Patients treated with flaxseed oil exhibited a significantly higher rate of return to sporting level before injury (P = 0.04) and a lower rate of occurrence of giving way (P = 0.04) than those in the placebo group. Patients with flaxseed oil showed significantly less severe adverse events on index knee (P = 0.047). Conclusion: The administration of dietary flaxseed oil enhanced the prognosis of acute ACL rupture.

Keywords: Anterior cruciate ligament rupture, flaxseed oil, surgical reconstruction

Introduction

The anterior cruciate ligament (ACL) is located in the knee joint [1]. Excessive forward displacement of the tibia is limited by ACL, which is the main stabilizing structure of the knee joint in both static and dynamic conditions [2]. Acute ACL rupture is defined as manifesting within less than 6 weeks from injury; chronic rupture is defined as manifesting after greater than 6 months (27 weeks) from injury. Acute ACL rupture is common in sports, due to sudden stopping, turning, or collision caused by athletes in fast running [3]. Among athletes, between 100,000 and 200,000 injuries occur each year and the average incidence is approximately 1 in 3500 [4]. Female athletes may be at greater risk than male athletes for ACL injury [5]. Injury of the ACL causes significant healthcare and financial burden and can result in loss of a sport season and sport scholarships, reduced academic performance, and long-term disability [6].

The traumatic mechanism of acute ACL rupture is mainly a translational force on the anterior of fixed leg [7]. Patients with acute ACL rupture present with pain, haemarthrosis, swelling, and motion instability [8]. If not treated in time, acute ACL rupture will compromise the stability of the knee, induce recurrent injury and associated intra-articular pathology, and restrict knee function with reduced activity level, affect life and labor, and contribute to increased osteoarthritis risk [9]. Thus, effective therapeutic strategies for acute ACL rupture are needed. In recent decades, the treatment of ACL rupture is based on medication and surgery, such as early surgical reconstruction [10], which is the most commonly used effective surgery treatment [11]. Conservative treatments for ACL rupture include the use of cryotherapy, continuous passive motion, restrictive bracing, electrotherapy, and exercises [9]. Even after good rehabilitation, 35% to 45% of injured athletes who receive ACL reconstruction do not return to pre-morbid levels [12]. Secondary ligament rupture, tech-

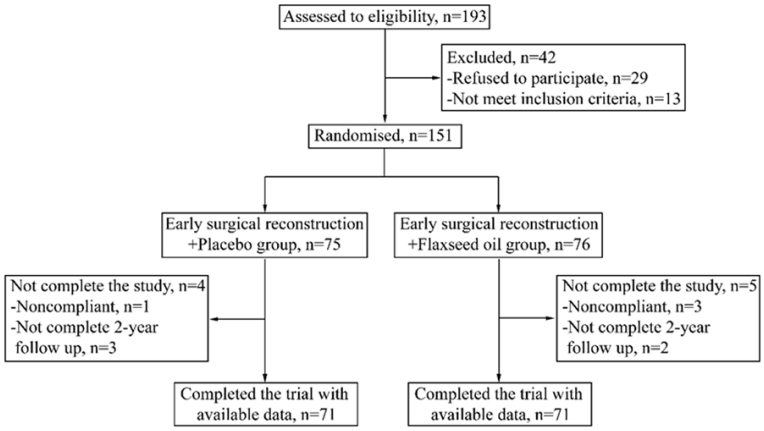

Figure 1. Flow chart of participants enrolled and follow-up.

nique and graft can lead to adverse outcomes including persistent instability, loss of motion, pain and osteoarthritis. Therefore, it is also important to reduce the possible risk factors for these adverse outcomes.

Clinical studies have shown that α-linolenic acid (ALA) exists in the form of glycerol esters in dark green plants, including flax, walnuts, *Spirulina* and *Chlorella* [13]. It is the main component of human tissue cells, which cannot be synthesized and metabolized in the body [14]. ALA can be transformed into docosahexaenoic acids (DHA) and eicosapentaenoic (EPA), which are essential life activity factors and play an important protective role against cardiovascular diseases [15]. Among vegetable oils, flaxseed oil has the highest ALA content (> 51%-65%) [16]. There are numerous studies exploring the effects of flaxseed oil on health. Flaxseed oil has promising cardioprotective properties and a flaxseed-supplemented diet has no significant side effects in older subjects [16-18]. In animal models such as mice, dietary flaxseed oil is widely reported to have benefits on bone development, inflammation suppression, alcoholic liver disease, and diabetic retinopathy [19-22]. This study aimed to explore whether dietary flaxseed oil has effects on the prognosis of patients receiving ACL reconstruction.

Methods

Patients

In this trial, patients aged 15-45 years with ligament injuries caused by sports, including ball sports, running, swimming, dancing, fitness and climbing, were recruited at Quanzhou First Hospital Affiliated to Fujian Medical University. This research was reviewed and approved by the institutional review board of Quanzhou First Hospital Affiliated to Fujian Medical University (2019.04.c3), and all the participants gave written consent.

The inclusion criteria were: patients between 15 and 45 years of age; patients with primary acute ACL rupture which was diagnosed through both magnetic resonance imaging and clinical examination; patients received and accepted the spoken and written standardized trial information. The exclusion criteria were: patients who had previous ACL injury on the contralateral knee; patients with other lower limb disorder; patients with dislocated bucket handle lesion of the meniscus with an extension deficit; patients who could not communicate in Chinese.

The participants were randomly divided into the placebo group and the flaxseed oil group by computer-generated random numbers before MRI scanning. The flowchart and follow up of the participants were shown in **Figure 1**. This trial was a double-blind study to avoid bias.

Intervention

In this study, patients in both groups received the same early reconstruction of the ACL. Arthroscopic reconstruction of the ACL in all patients was performed by experienced surgeons with the same methods and materials in the same department. The choice of technique and graft was made by the surgeon and a decision was made if additional intra-articular surgery was necessary. Patients would undergo physical therapy to re-establish motor function following the procedure.

Patients received the daily administration of placebo or flaxseed oil capsules for two years after surgery. Corn oil which contains relative low level of ALA and was not reported to function on ACL was administrated as the placebo.

Patients in the placebo group took six corn oil capsules (9 g) daily. Patients in the flaxseed oil group took six flaxseed oil capsules (9 g flaxseed oil with 4.2 g ALA) (Kang Hui Zhong Tian Technology) daily. All patients were asked to take the capsules continuously for 2 years and fill a chart to record each administration every day. In addition, their compliance had been confirmed every two weeks by contacting on the phone.

Outcomes

The patients were evaluated once by the following evaluations through a questionnaire of each scale at 2 years after the early reconstruction of the ACL.

The Knee Injury and Osteoarthritis Outcome Score (KOOS) has five subscales for sports, pain, quality of life, activities of daily living, and symptoms. The KOOS score ranges from 0 to 100, with an optimum score of 100.

International Knee Documentation Committee (IKDC) score is composed of 18 items (7 symptom items, 9 daily activity items, 1 current knee function item, and 1 sport activity item). The score of IKOC ranges from 0 to 100, and the optimum score is 100.

The Lysholm Knee Scoring Scale is composed of eight sections (pain, instability, catching, swelling, stair-climbing, squatting, limping, and the need of support). The optimum score is 100.

The Tegner Activity Scale is an additional instrument for the Lysholm score which evaluates sport and work activity. The Tegner score ranges from 0 to 10, and the optimum score is 10.

Statistical analysis

SPSS 22.0 was used for data analysis. Data were expressed as n (percentage, %) or mean ± standard deviation (SD). Proportions were compared using Chi-square (χ^2) test. Means for the two groups were compared using Mann-Whitney test. $P < 0.05$ was considered significant.

Results

The clinical and demographic data of the participants are shown in **Table 1**. Notably, data from those that did not complete the study due to noncompliance or lost to follow-up in the 2 years were not analyzed in this study. These two groups were homogenous for gender, age, education, body mass index (BMI), cause of injury, MRI findings, interval between injury and inclusion, IKDC, KOOS, Lysholm, and Tegner scores (all $P > 0.05$).

Two years after surgery, patients showed increased IKDC score in both the placebo group (78.3 vs 43.8) and the flaxseed oil group (83.3 vs 48.6). When compared with the placebo group, flaxseed oil group displayed significantly higher IKDC score after the two-year administration (83.3 vs 78.3, $P = 0.02$) (**Table 2**). Meanwhile, based on the results of KOOS score, patients treated with flaxseed oil exhibited significantly higher scores in sports and recreation (88.9 vs 81.3, $P = 0.01$), knee-related quality of life (75.8 vs 68.2, $P = 0.03$), and the total score of KOOS (86.4 vs 82.0, $P = 0.0003$), than those in the placebo group (**Table 2**).

We also evaluated several secondary outcomes after the two-year administration. As shown in **Table 3**, patients in the two groups showed no significant differences in Tegner score (6.96 vs 6.60, $P = 0.15$), Lysholm score (88.9 vs 85.9, $P = 0.07$), or the rate of treatment satisfaction (93.0% vs 88.7%, $P = 0.38$). However, patients treated with flaxseed oil reported significantly higher rate of return to sporting level before injury (56.3% vs 39.4%, $P = 0.04$) and significantly lower rate of occurrence of giving way (4.2% VS 14.1%, $P = 0.04$) than those in the placebo group (**Table 3**).

Furthermore, the occurrence of severe adverse events during the two-year administration was also evaluated. As shown in **Table 4**, patients in the flaxseed oil group showed significantly less severe adverse events on the index knee (17 VS 28, $P = 0.047$).

Discussion

In this trial, we demonstrated that supplemental dietary flaxseed oil has positive effects on enhancing the clinical results and alleviating severe adverse events two years following surgical reconstruction of acute ACL rupture.

In recent years, studies have demonstrated various functions of Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) in promoting human

Table 1. Baseline characteristics of participants

	Placebo (n = 71)	Flaxseed oil (n = 71)	*P* value
Female/male (n/n)	24/47	21/50	0.59[a]
Age, median (range)	31 (15-45)	30 (15-44)	0.28[b]
College education or equivalent, n (%)	23 (32.3)	25	0.72[a]
Body mass index, median (range)	21.9 (16.0-28.9)	23.7 (16.1-29.0)	0.15[b]
Injury of left knee, n (%)	34 (47.9)	38 (53.5)	0.50[a]
Cause of injury			
Boll sport, n (%)	45 (63.4)	42 (59.2)	0.73[a]
Other sport, n (%)	26 (36.6)	29 (40.8)	0.73[a]
MRI findings			
Total ACL rupture, n (%)	71 (100)	71 (100)	1.00[a]
Meniscal injury, n (%)[*]	45 (63.4)	40 (56.3)	0.39[a]
Time between injury and inclusion, mean (SD)	40.4 (15.8)	39.7 (16.4)	0.75[b]
IKDC score, mean (SD)[++]	43.8 (9.8)	43.6 (10.2)	0.93[b]
KOOS score[※]			
Pain, mean (SD)	61.7 (21.3)	62.56 (20.6)	0.81[b]
Symptoms, mean (SD)	48.5 (26.2)	48.7 (25.8)	0.98[b]
Function in activities of daily living, mean (SD)	66.0 (18.7)	66.8 (18.4)	0.81[b]
Function in sports and recreation, mean (SD)	20.8 (18.4)	20.1 (18.8)	0.74[b]
Knee-related quality of life, mean (SD)	28.6 (21.4)	28.6 (22.3)	0.98[b]
$KOOS_4$ score, mean (SD)[&]	44.5 (12.2)	44.8 (11.5)	0.90[b]
Tegner score before injury, mean (SD)[#]	8.2 (1.4)	8.3 (1.5)	0.69[b]
Lysholm score, mean (SD)[$]	62.5 (13.3)	62.4 (13.3)	0.87[b]

[*]Meniscal injury was classified as increased signal extending to at least one articular surface of the meniscal body. [++]IKDC score: International Knee Documentation Committee score, optimum score 100. [※]KOOS: Knee Injury and Osteoarthritis Outcome score (range 0-100; optimum score 100). [&]KOOS4 includes four KOOS subscales: pain, symptoms, function in sports and recreation, and knee-related quality of life. Scores range from 0 to 100, with higher scores indicating better results. [#]The Tegner Activity Scale assesses activity level with specific emphasis on the knee. [$]Lysholm score (range 0-100). [a]χ^2 test. [b]Mann-Whitney test.

health and reducing disease risk [23]. ω-3 PUFAs include stearidonic acid (SDA), ALA, DHA, and EPA. Although the major source of ω-3 PUFAs is marine organisms, several kinds of seeds are also good ω-3 PUFAs sources [24]. ALA is an 18-carbon essential unsaturated FA. For ALA, the seeds of flax and canola, and echium seed oils are reported to be good sources [15]. In the human body, ALA is the precursor of LC PUFAs, including DHA and EPA [25]. Based on different gender and age, the required ALA level is 1.1-1.6 g/day for the prevention of deficiency symptoms [13]. Among canola, flaxseed, soybean and walnut oils, flaxseed oil contains the highest ALA content (49.2 g/100 g) [26]. Since ω-3 and ω-6 PUFAs can form eicosanoids through lipoxygenases, cyclooxygenases and cytochrome P450 monooxygenases, they are involved in the process of pathogenesis [27]. ω-6 PUFA derivatives are pro-inflammatory, whereas ω-3 PUFA has a partial inhibitory effect on inflammation and competes with ω-6 PUFA for the corresponding enzymes [28]. Increased dietary ω-3 PUFA may regulate the balance of eicosanoid production [29] and gene expression to suppress inflammation [30].

ACL fractures lead to joint instability, reduced mobility and quality of life, as well as increased osteoarthritis risk of the knee [31]. Osteoarthritis from joint injury leads to synovitis, subchondral bone remodeling, and articular cartilage degeneration [32]. Studies have confirmed that imbalanced PUFA in human body leads to enhanced pain and reduced knee function [33]. The ACL transection (ACLT) model confirms that ACL injury enhances inflammatory mediator production [34]. Research has suggested that the balance of ω-3 and ω-6 PUFAs is altered by ACL transection [30]. Changing ω-3/ω-6 PUFA

Table 2. Primary outcomes at 2 years

	Placebo (n = 71)	Flaxseed oil (n = 71)	*P* value
IKDC score, mean (SD)	78.3 (13.7)	83.3 (10.6)	0.02[b]
Change in IKDC score, mean (SD)	34.6 (9.7)	40.8 (11.6)	0.001[b]
KOOS score			
Pain, mean (SD)	87.3 (13.0)	87.6 (13.3)	0.96[b]
Symptoms, mean (SD)	83.4 (19.6)	89.3 (9.1)	0.41[b]
Function in activities of daily living, mean (SD)	91.3 (10.6)	93.9 (7.3)	0.33[b]
Function in sports and recreation, mean (SD)	81.3 (17.8)	88.9 (11.5)	0.01[b]
Knee-related quality of life, mean (SD)	68.2 (22.0)	75.8 (19.9)	0.03[b]
$KOOS_4$ score, mean (SD)	82.0 (8.2)	86.4 (6.7)	0.0003[b]
Change of $KOOS_4$ score, mean (SD)	37.4 (12.4)	41.7 (12.2)	0.07[b]

[b]Mann-Whitney test.

Table 3. Secondary outcomes at 2 years

	Placebo (n = 71)	Flaxseed oil (n = 71)	*P* value
Tegner score, mean (SD)	6.6 (1.4)	6.96 (1.2)	0.15[b]
Lysholm score, mean (SD)[*]	85.9 (11.4)	88.9 (10.6)	0.07[b]
Return to sporting level before injury, n (%)	29 (39.4)	39 (56.3)	0.04[a]
Occurrence of giving way, n (%)	10 (14.1)	3 (4.2)	0.04[a]
Satisfied with treatment, n (%)	63 (88.7)	66 (93.0)	0.38[a]

[*]Lysholm score (range 0-100; optimum score 100). [a]χ^2 test. [b]Mann-Whitney test.

Table 4. Serious adverse events during the 2 years

	Placebo (n = 71)	Flaxseed oil (n = 71)	*P* value
Site other than index knee	10	9	0.80[a]
Musculoskeletal	2	1	
Cardiovascular	3	2	
Skin	1	2	
Gastrointestinal	2	2	
Nervous	1	1	
Others	1	1	
Index knee	28	17	0.047[a]
Subjective or clinical instability[*]	11	7	
Meniscal signs and symptoms	9	6	
Pain, swelling, or both	3	1	
Decreased range of motion	2	1	
Extension deficit	1		
Arthrofibrosis		1	
Graft rupture	1		
Other	1	1	
Total serious adverse events	38	26	0.043[a]

This table includes serious adverse events that were those classified as having the potential to significantly compromise clinical outcome or result in significant disability or incapacity; those requiring inpatient or outpatient hospital care; and those considered to prolong hospital care, to be life-threatening, or to result in death. [*]Subjective instability was reported by the subject. Clinical instability was defined as anteroposterior instability, as determined by the Lachman test (grade 1 or higher), or rotational instability as determined by the pivot shift test (grade 1 or higher). [a]χ^2 test.

ratio in diet is an effective non-pharmaceutical approach of improving systemic inflammation [35]. Therefore, the aim of this research was to determine whether dietary addition of ALA-rich flaxseed oil could improve postoperative recovery of ACL rupture.

The IKDC and the KOOS scores are two commonly used site-specific patient-reported outcome instruments for the knee [36, 37]. The IKDC score has been widely used to clinically assess the outcome of ACL reconstruction and is also the most common patient-reported outcome measure for patients with ACL defects [38]. The KOOS score is a relatively new patient-reported outcome measure developed in Sweden and is increasingly used in clinical ACL reconstruction studies [39]. In recent years, studies have been performed using both IKDC and KOOS to assess ACL defects [40, 41]. The elevated scores of IKDC in both groups by the two-year treatment indicated better clinical results. The

patient-reported outcomes of patients with ACL rupture after surgical reconstruction were enhanced in both groups. However, the higher IKDC score in the flaxseed oil group indicated a better prognosis of ACL rupture.

The total score of KOOS also showed the same tendency. The KOOS is consisted of five subscales, including pain, symptoms, function in activities of daily living, function in sports and recreation, and knee-related quality of life. Based on the results of these subscales, the treatment with flaxseed oil showed no effects on pain, symptoms, and function in activities of daily living after the surgery. However, after two years, patients treated with flaxseed oil showed better function in sports and recreation and higher knee-related quality of life. Thus, dietary supplementation with flaxseed oil was effective in promoting the prognosis of acute ACL rupture.

Furthermore, we evaluated the secondary outcomes of patients with ACL rupture after the 2-year treatment. The Lysholm score was published in 1982 and was used to manage and measure outcomes after knee ligament surgery, emphasizing the assessment of instability [42]. In 1985, the Tegner Activity Scale was developed to complement the Lysholm score [43]. This new scale grades activity according to work and physical activity [43]. The Lysholm score and Tegner Activity Scale have been well validated and tested for reliability in patients with anterior cruciate ligament (ACL) injury, with good criterion validity and retest reliability [44]. In our study, both the Lysholm score and Tegner Activity Scale showed that the secondary outcomes of the patients with ACL reconstruction were not significantly enhanced by flaxseed oil. However, the administration of flaxseed oil elevated the proportion of patients who returned to sporting level before injury. The occurrence of giving way in patients with ACL reconstruction was reduced by supplemental dietary flaxseed oil. Another result in this research demonstrated that the administration of different oil exhibited no significant influence on the patients' satisfaction with treatment.

Severe adverse events during the 2 years were also analyzed in this research. In patients with ACL rupture following surgical reconstruction, the number of severe adverse events at a site other than the index knee was not affected by the administration of flaxseed oil. However, supplemental dietary flaxseed oil significantly decreased severe adverse events on the index knee of patients with ACL rupture following surgical reconstruction. Thus, the administration of flaxseed oil decreased the severe adverse events on the index knee of patients with ACL rupture.

There were some limitations in this research. First, inflammation caused by the ligament rupture was considered. The reconstructive and surgical procedures might also induce inflammation. Furthermore, this research focused on the effect of flaxseed oil on the reconstruction of ACL rupture. In future work, whether similar mechanisms from taking the flaxseed oil also occur in the surgery of other ligament ruptures should be investigated. Whether the outcomes after ACL reconstruction varied according to graft type should also be explored. Owing to the limited number of patients, we did not set up the blank control group, which could provide more convincing evidence to exclude the influence of placebo and make the conclusion more solid. We recommend that blank control group should be included in future larger scale trials.

In conclusion, the administration of dietary flaxseed oil enhanced the prognosis in acute ACL rupture.

Acknowledgements

This research was reviewed and approved by the institutional review board of Quanzhou First Hospital Affiliated to Fujian Medical University, and all the participants gave written consent.

Disclosure of conflict of interest

None.

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