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Effects of Flaxseed Oil and Olive Oil on Markers of Inflammation and Wound Healing in Burn Patients: A Randomized Clinical Trial

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ABSTRACT

Objectives: To study the anti-inflammatory and antioxidant effects of flaxseed oil and olive oil on inflammatory markers for facilitating wound healing.
Methods: One hundred and twelve patients were randomly selected to four groups with a total burn surface area (TBSA) of 20-50%. The four groups includes olive oil (OO), flaxseed oil (FO), mixture of olive oil and flaxseed oil (OF), and control group and received 30g of oils for three weeks. Serum high-sensitivity C-reactive protein (hs-CRP), ferritin and albumin level as inflammatory markers, as well as cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) as the lipid profile were explored. Wound healing was assessed by photographing on days 2, 8, 15, and 22 (during three weeks of intervention) and were analyzed in imageJ software.
Results: The greatest reduction in the level of hs-CRP and ferritin was observed in the OF (-21.38±44.41) (-132.79±165.36), while the lowest reduction was reported in the control group (-36.36±79.03) (141.08±262.36). Compared to control group, OO significantly increased albumin (0.88±0.65). Reduction of wound healing at the end of the first week of intervention was not significant in the study groups. However, the stereology examination showed significant improvement in wound healing at the end of the second and third weeks in the OF.
Conclusion: Based on the findings, combination of herbal oils reduce inflammation and improve wound healing and showed positive effects on the size of wounds in burn patients.

Keywords: Flaxseed oil; Olive oil; Burn; Wound; Inflammation indices.

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Introduction

Burns as a global public health concern, account for an estimated number of 180,000 deaths annually [1]. They are among the most important causes of morbidity and mortality in patients, which have significant economic and social consequences for human societies [2]. The majority of burns occur in low- and middle-income countries, and almost two-thirds of burns occur in African and Southeast Asian countries [3]. In Iran, burns are the 8th most common cause of mortality and the 13th most common cause of disability [4]. According to the reports, 250000 people are burning every year and account for an estimated 180000 deaths annually. Nearly 23750 burn injuries were reported in Iran between 2012 and 2015 [2, 5, 6]. In developed countries and due to the limited resources, it is difficult to manage burn injuries and complications from these patients, which is one of the main causes of patient's mortality [3].

Burns can cause both local and systemic inflammation that affect the wound healing process, as well as hemodynamic changes on the skin, blood vessels, and blood components [7]. Impairment of metabolic, inflammatory, endocrine, and immune responses can predispose patients to malnutrition, wound healing, muscle erosion, severe weight loss, and frequent infections [8], leading to long-term hospitalization and increased length of stay in the intensive care unit (ICU) [9]. On the other hand, proper nutrition include health fats improves wound healing and diminishes the effects of severe metabolic responses [9]. Omega-3 (n-3) fatty acids, which are not synthesized in the body [10], and omega-6 (n-6), as polyunsaturated fatty acids (PUFAs), play significant roles in wound healing and improvement of immune responses by reducing the production of synthetic inflammatory proteins in burn patients [9-11].

Generally, various markers can predict inflammation [9]. Studies have demonstrated that marine-derived omega-3 supplementation had significant effects on the reduction of C-reactive protein (CRP) [12, 13]. CRP is one of the oldest indicators of acute-phase response [14], that is correlated with the size and depth of burn [15]. In addition, albumin level was recognized as an indirect inflammatory marker and changes in the level of albumin. These are reliable indicators of increased or decreased inflammation [9]. Moreover, ferritin is a ubiquitous protein containing iron, which increases under certain conditions such as inflammation and is a well-known acute phase protein that reflect the degree of acute and chronic inflammation. Compelling evidence suggest a potential active role of ferritin in inflammatory diseases [16]. It is known that reduction of high-sensitivity C-reactive protein (hs-CRP) and ferritin levels, besides an increase in albumin content, can reduce inflammation [17].

Olive oil is rich in unsaturated fatty acids and exhibits antioxidant properties. It contains 98% triglyceride, 18% omega-6 (linoleic acid), and 63% omega-9 (oleic acid). It is effective for wound healing due to its anti-inflammatory and anti-oxidative properties [18, 19]. Olive oil compounds have a lot of benefit effects in healing burned skin [7]. In addition, it ameliorates the inflammation process due to the high concentration of polyphenols as natural antioxidants. The key role of oleic acid in the repair of cell membranes is to increase the skin moisture and elasticity [19, 20]. *Linum usitatissimum* is an annual plant of linseed family, which is commonly found in the Mediterranean region. Flaxseed is well known for its richness in alpha-linolenic acid (ALA, 18:3n-3), it is considered to be the most superior source of ω-3, crude fiber, proteins, and antioxidants. Useful flax fat is accumulated in the plant oil [21-23]. Accumulating studies have shown that flaxseed oil protects against inflammation [24] and via suppressing inflammation can accelerate wound healing [19, 25].

Various medications includes chemical and herbal drugs have been utilized with the aim of wound healing acceleration [26] and despite the great advances in medical sciences, the role of nutrition in the treatment of patients with a critical conditions is often ignored [19]. No human study has investigated the effect of inexpensive, accessible and nutritious foods such as olive oil with or without flaxseed oil in burn patients to help treating wound burn in patients through cost-effective and practical methods and reduce the financial burden of this disease. In this study, the anti-inflammatory and antioxidant properties of these two herbal oils, as well as their availability for all patients, encouraged us to evaluate the use of herbal oils for wound healing.

Materials and Methods

Participants

In this double-blind, parallel-group, randomized clinical trial, a total of 112 patients with deep second-degree wounds were selected from Velayat Sub-Specialty Burn and Plastic Surgery Center in Guilan Province, Rasht, Iran, using block randomization. The ethics board of Guilan University of Medical Sciences, Rasht, Iran, approved the study protocol (reference number: IR.GUMS.REC.1395.501). All patients provided written informed consents and all procedures were in accordance with the tenants of the Declaration of Helsinki and its later amendments [27]. This trial was registered at http://www.irct.ir as IRCT20080901001174N11.

The inclusion criteria were as follows: burn degree of 20-50% of total body surface area (TBSA); patients with thermal or chemical burns; hospitalization within 24 hours post-burn; age range of 15-65 years; body mass index (BMI) of 18–30 kg/m2; ability to eat and drink through the mouth; and willingness to participate in the study. On the other hand, patients with renal or hepatic failure, diabetes mellitus, connective tissue disorders, malnutrition on admission, allergy to olive or flaxseed oil, use of omega-3 or omega-6 fatty acids in the last month, or need for parenteral or enteral nutritional support and mechanical ventilation support were excluded from the trial. The patients were enrolled between May 2018 and February 2019.

Among 739 patients who were initially enrolled in this study, 114 met the inclusion criteria and entered the study. However, two patients died on day 5 and day 10 because of septicemia (Figure 1).

Randomization

The participants were assigned to four equal groups (1:1:1:1): olive oil (OO), flaxseed oil (FO), mixture of olive oil and flaxseed oil (OF), and control group. Block randomization was carried out with variable block sizes at a ratio of 1:1:1:1, using a computer algorithm (www.randomization.com).

Intervention

Extra virgin olive oil extracted from olives and flaxseed oil extracted from flaxseed were prepared by household oil press machines. Analysis of fatty acid profile, antioxidants, and polyphenols was performed using a gas chromatography–mass spectrometry (GC/MS) machine at Rahymi Chemical Specialty Laboratory (www.afshinrahimilab.com) (Table 1).

In this double-blind study, odorless olive oil and flaxseed oil were kept in dark glass bottles with no tags. Neither patients nor nutritionists knew about the type of oil. It should be noted that the color of both oils was golden yellow. Generally, flaxseed oil has little odor for seven days and cannot be distinguished from odorless olive oil. All patients provided written informed consents. The participants were asked to avoid nutritional supplements or high-phytate foods during treatment. After admission, all patients received conventional wound management, fluid replacement, and nutrition advice.

Group OO (n=28) received 30cc of olive oil, group FO (n=28) received 30cc of flaxseed oil and Finally, group OF (n=28) used 15 cc of flaxseed oil mixed in 15 cc of olive oil in a salad daily as a meal for 21 consecutive days. Group C (n=28), as the control group, had a salad without oil as a meal daily for 21 consecutive days. The salad ingredients were adjusted by a nutritionist to suit each patient and were calculated according to the Curreri formula of energy. The diet contained 24% protein calories, 27% fat, and 49% carbohydrates. At the time of discharge, the patients were given unnamed dark glass containers of oils. The correct amount of oil was accurately written and monitored daily by a nutritionist via telephone calls.

Primary and Secondary Outcome Measurements

On the morning of the second day of admission, a blood sample was taken from each patient after

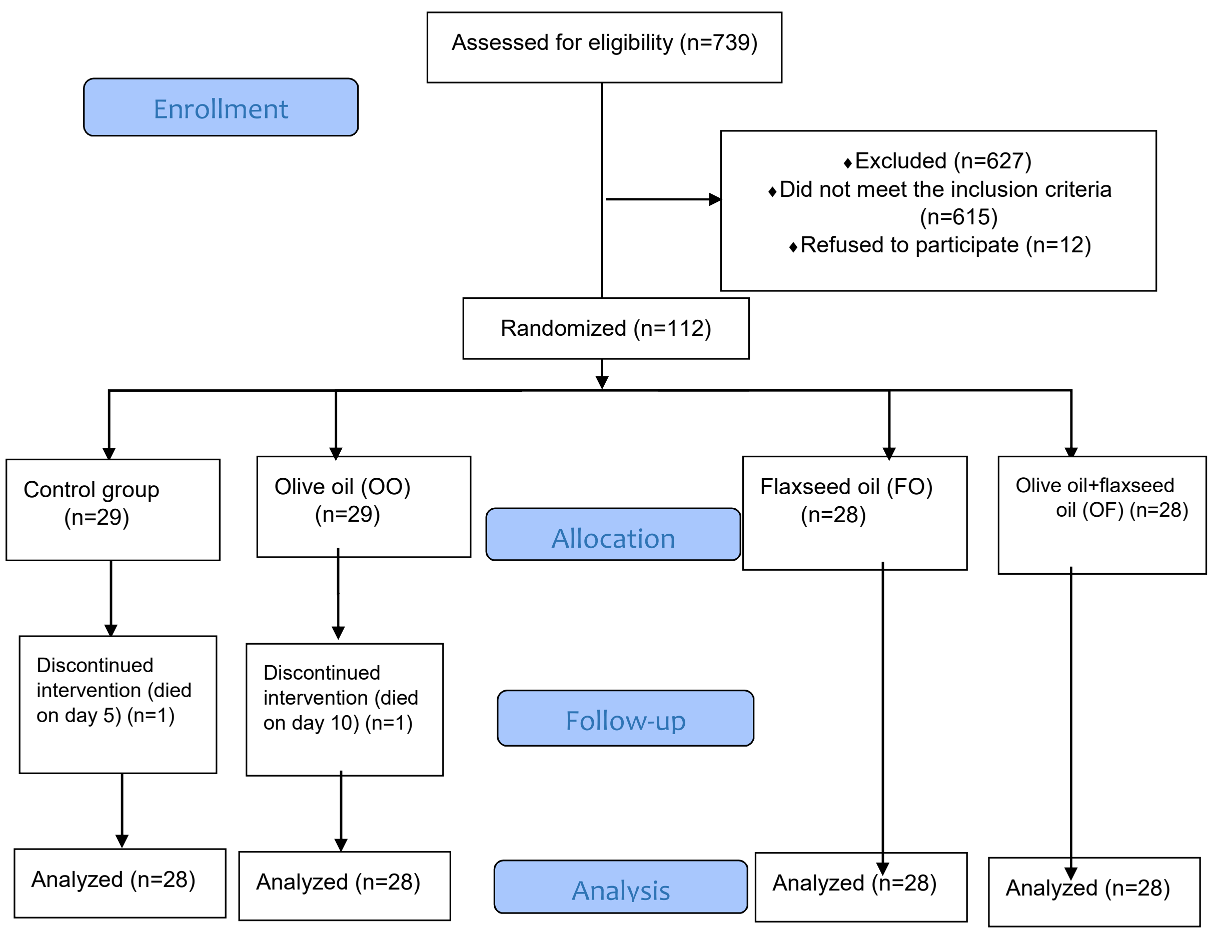

Fig. 1. CONSORT flow diagram of subject enrollment, allocation, follow-up, and analysis.

Table 1. Fatty acid composition of diets (1000 kcal).

Nutrients	Olive oil	Flaxseed oil
Saturated fatty acids	15.05994	9.89848
Polyunsaturated fatty acids	84.94005	90.10153
Palmitic acid	10.86555	5.10993
Palmitoleic acid	0.84159	0.53205
Oleic acid	70.45692	21.25151
Linoleic acid	12.64544	15.88714
Arachidic acid	0.52698	0.18251
γ-Linolenic acid	0.9141	52.96288

eight hours of fasting. Blood tests included hs-CRP, ferritin, albumin, complete blood count (CBC), cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood glucose (FBS). The serum hs-CRP level was measured using an enzyme-linked immunosorbent assay (ELISA) kit (INS, BIOMERICA, USA). Ferritin level was also measured using an ELISA kit (Pishtaz Teb Diagnostics, Tehran, Iran), and serum albumin was determined by the bromocresol green method (Pars Azmoon Co., Tehran, Iran). On the 22nd day of admission, blood samples were collected from the patients, and the blood tests were repeated. If the patient was discharged on this day, he/she was referred to the hospital laboratory for sampling.

The wound size was measured by imaging the wounds and examining the appearance of ulcers. To determine the extent of wound closure, all of the wound surface was imaged on days 2, 8, 15, and 22 and then processed in ImageJ software [28, 29] (Figure 2). Also, reduction of the wound area and improvement of wound size were recorded. A Canon camera and a standard ruler were used for this purpose.

Nutritional Status Assessment

Height and weight of the patients were measured, and body mass index (BMI) was calculated as the person's weight in kilograms, divided by height in meters squared (kg/m^2). Weight was measured using an electronic scale (Beurer PS240, Germany) to the nearest 0.1 kg. All anthropometric measurements were performed twice and averaged. If the difference between two measurements was greater than 1.0 cm or 0.1 kg, a third measurement was taken, and the two closest values were averaged. The patients' height was also measured in centimeters. Moreover, the patients' nutritional information was completed at the beginning of the study, using a 24-hour dietary recall (24HR).

Statistical Analysis

We selected a sample size of 28 per group with the assumption of hs-CRP as the primary outcome at 80% power, two-sided alpha level of 0.05, and 10% attrition rate. The subjects' characteristics, dietary intake, and blood indices (hs-CRP, ferritin, and albumin) at baseline were compared between the groups, using one-way ANOVA, Chi-square, and Kruskal-Wallis test (Table 2). Comparisons between the stereological outcomes were carried out using Bonferroni test. Kruskal-Wallis test was also used to determine the effect of treatment on wound healing over time (from day 2 until day 22). Data are expressed as mean±SD. Statistical analyses were performed in SPSS version 23 (Statistics analysis was conducted using the SPSS software package (version 23.0, SPSS Inc, Chicago, IL, USA). *P* values of less than 0.05 determined the statistically significant.

Results

The results showed that from 112 patient, 27 (24.10%) patients were women, and 85 (75.89%) patients were men. The mean age of the participants was 43.25±13.25 years. It was found that the most

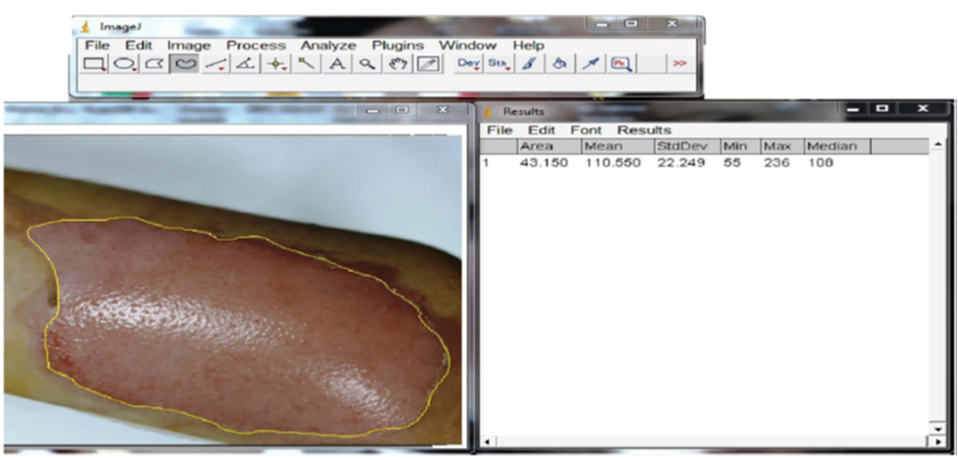

Fig. 2. Measurement of photographs of wounds and their evaluation with ImageJ.

Table 2. Demographic characteristics of the control and intervention groups at baseline[a].

Characteristics		Olive oil (OO) (n=28)	Flaxseed oil (FO) (n=28)	Control group (n=28)	Olive oil+flaxseed oil (OF) (n=28)	*p* value
Sex	Male	23	21	22	19	0.635*
	Female	5	7	6	9	
Age (years)		43±13	43±12	45±15	42±13	0.816[j]
BMI[b] (kg/m^2)		26.2±3.9	25.6±3.8	25.8±3.4	24.6±3.6	0.451[k]
TBSA[c] (%)		29±10	31±10	29±10	31±10	0.872[l]
smoking(n)		12	10	12	15	0.604[k]
Grafted patients (n)		21	23	24	25	0.3[k]
Grafted day		9.18±2.62	10.32±3.37	9.89±2.93	9.32±2.76	0.3[l]
SBP[d] (mmHg)		124.0±16.0	124.5±13.6	126.8±17.6	123.0±14.7	0.824[l]
DBP[e] (mmHg)		76.8±7.3	76.1±8.6	76.9±9.3	75.9±7.2	0.937[l]
Dietary intake[f]						
Energy (kcal/day)		2351.5±795.9	2902.1±647.5	2547.1±585.2	2039.3±707.7	<0.001
Protein (g/day)		91.44±41.45	115.64±30.03	101.31±34.16	84.72±43.55	0.002
Carbohydrate(g/day)		318.35±115.79	389.75±91.25	331.63±87.21	272.75±90.51	<0.001
Fat (g/day)		79.91±46.36	101.34±36.39	94.88±45.35	69.88±27.85	0.006
SFA[g] (g/day)		18.14±8.66	27.33±14.46	23.84±13.44	18.40±8.92	0.007
MUFA[h] (g/day)		18.54±10.78	26.02±9.85	23.82±14.04	18.08±7.67	0.007
PUFA[i] (g/day)		38.215±25.091	38.777±21.552	37.736±21.288	25.203±15.684	0.054

[a]Data are presented as mean±SD or frequency; [b]BMI: Body Mass Index; [c]TBSA: Total Body Surface Area; [d]SBP: Systolic Blood Pressure; [e]DBP: Diastolic Blood Pressure; [f]Between-group differences are examined using Kruskal-Wallis test; [g]SFA: Saturated Fatty Acids; [h]MUFA: Monounsaturated Fatty Acids; [i]PUFA: Polyunsaturated Fatty Acids; [j]Chi-square test; [k]Fisher's exact test; [l]ANOVA test.

Table 3. Alterations in serum proteins, lipid profile, and inflammatory markers of patients during the intervention[a].

Characteristics		Total (n=112)	Olive oil (OO) (n=28)	Flaxseed oil (FO) (n=28)	Control group (n=28)	Olive oil+flaxseed oil (OF) (n=28)	*p* value[b]
Albumin (g/dL)	Before	3.14±0.79	3.09±0.84*	2.98±0.73	3.41±0.85	3.09±0.77	0.247
	After	3.62±0.42	3.97±0.58	3.36±0.30	3.59±0.53	3.57±0.51	<0.001
	Change	0.48±0.63	+0.88±0.65	+0.38±0.55	+0.18±0.79	+0.48±0.56	0.003
Ferritin (ng/mL)	Before	323.7±169.7	319.79±137.33	347.66±196.94	298.12±157.20	329.39±187.67	0.768
	After	290.8±159.1	246.21±117.21	281.38±149.82	439.19±232.28	196.61±137.31	<0.001
	Change	103.4±162.3	-73.57±110.75	-66.28±110.84	+141.08±262.36	-132.79±165.36	<0.001
hs-CRP[c] (mg/mL)	Before	58.5±47.5	52.75±38.16	64.07±49.86	62.79±58.48	54.59±43.62	0.879
	After	54.8±43.6	39.86±31.51	47.31±41.94	99.15±65.80	33.21±35.41	<0.001
	Change	21.8±46.1	-12.89±29.96	-16.77±31.04	+36.36±79.03	-21.38±44.45	0.001
Cholesterol	Before	143.3±60.7	169.21±83.69	154.25±76.25	123.46±43.48	126.36±39.54	0.072
	After	161.3±110.3	162.89±93.10	180.39±180.39	179.11±108.75	123.11±59.27	0.021
	Change	22.8±94.2	-6.32±124.59	+26.14±79.08	+55.64±112.43	-3.29±60.89	0.023
Triglyceride	Before	130.5±52.6	136.36±51.23	139.39±76.25	112.68±43.48	133.96±39.54	0.362
	After	139.6±80.9	127.68±65.74	140.82±89.99	150.86±108.75	139.14±59.27	0.486
	Change	13.3±83.6	-8.68±82.01	+1.43±79.08	+38.18±112.43	-5.18±60.89	0.013
HDL[d]	Before	34.6±25.47	37.46±15.71	35.39±13.63	30.12±63.20	35.46±9.36	0.084
	After	42.0±13.9	46.00±15.33	41.82±12.53	35.07±14.38	45.14±13.64	0.010
	Change	7.3±14.135	+8.54±17.75	+6.43±12.04	+4.86±12.29	+9.68±14.46	0.552
LDL[e]	Before	72.54±26.71	76.79±27.44	80.07±28.92	65.86±24.03	67.46±26.46	0.172
	After	71.85±33.74	66.14±21.13	77.82±23.46	80.11±24.21	63.36±66.00	0.010
	Change	7.81±22.10	-10.64±26.70	-2.25±22.91	+14.25±27.05	-4.11±11.75	<0.001
FBS[f]	Before	176.7±73.74	152.07±58.04	175.61±68.42	186.68±88.01	192.46±80.50	0.222
	After	122.75±34	114±25	126±34	134±46	117±31	0.194
	Change	49.01±57.14	-38.54±44.39	-49.89±56.77	-52.86±62.36	-75.71±65.04	0.233
Wound area	diff 2-8[g]	9.74±48.30	19.81±30.9	7.39±49.07	-3.72±66.93	8.06±46.32	0.262
	diff 2-15[g]	64.36±56.27	65.12±48.15	49.33±48.61	113.2±65.37	29.79±62.95	<0.001
	diff 2-21[g]	137.96±92.01	117.2±161.4	135.1±66.2	213.7±79.07	85.84±61.40	<0.001

[a]Data are presented as mean±SD; [b]Between-group differences are examined using Kruskal-Wallis test; [c]hs-CRP: C-Reactive Protein High-Sensitivity; [d]HDL: High-density lipoprotein; [e]LDL: Low-density lipoprotein; [f]FBS: Fasting Blood Sugar; [g]The difference in wound area before intervention (2^d day) to after intervention (8^{th} day) (cm^2).

common burn sites were the upper limbs, and the most common cause of burn was thermal burn (91.96%). There was no significant difference in the baseline characteristics of the groups (Table 2).

Nutrition variables were significant in the four groups. However, since the diet of each patient was prepared by the nutritionist according to his/her nutritional status, and the calorie, protein, carbohydrate, fat, micronutrient, and macronutrient intakes were individually decided, they had no significant effects on the results. All patients were grafted as necessary, and there was no significant difference between the groups. The results showed that none of the patients had digestive complications such as gastrointestinal intolerance or allergies to food.

Inflammatory Markers

Concentrations of serum proteins and inflammatory markers at baseline and after the intervention are shown in Tables 2 and 3. After the intervention (on the 22nd day) the greatest increase in albumin was observed in the olive oil group (p=0.003) and the most decrease of hs-CRP levels and ferritin was in the oil mixture group (p<0.001) rather than the other groups. Therefore, consumption of olive oil with or without flaxseed oil is significantly effective in reducing ferritin and hs-CRP levels compared to the control group, while this effect was significantly higher in the mixture of oil group (Table 3) (Figure 3). Also, olive oil with or without flaxseed oil reduced cholesterol and triglyceride levels, while an increase was reported in these markers in the flaxseed oil and control groups.

Wound Healing

The wound area (cm^2) was assessed on days 2, 8, 15, and 22. All groups demonstrated a significant reduction in the wound area over three weeks (p<0.001). Reduction of the wound area between days 2 and 8 was zero in the control, flaxseed oil, and flaxseed oil+olive oil groups (95% CI for zero variation), whereas in the olive oil group, changes were greater than zero; however, there was no significant difference between the four groups. Moreover, the wound area significantly decreased in the flaxseed oil+olive oil group between day 2 and day 15 and the difference was significant between the four groups. The greatest reduction was observed in the flaxseed oil+olive oil group. Also, changes in the wound area were more dramatic in the flaxseed oil+olive oil group from day 2 to day 22, compared to the other groups, and the difference was statistically significant (Figure 4).

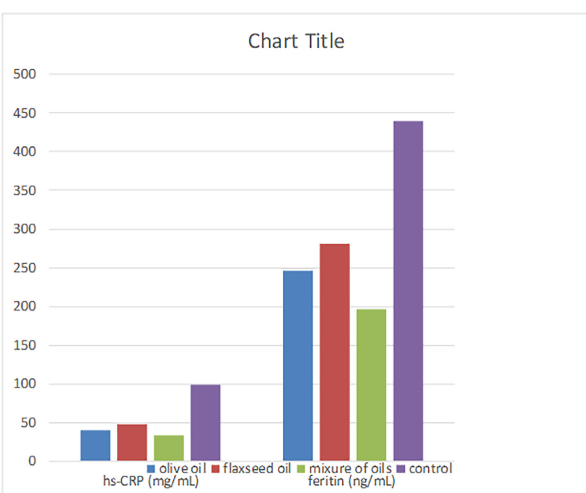

Fig. 3. Comparison of ferritin and high-density lipoprotein (hs-CRP) levels after intervention.

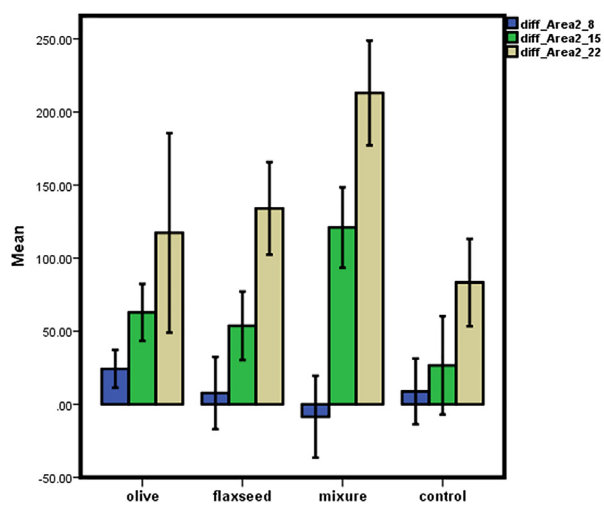

Fig. 4. Improvement in the percentage of burn wound area over time (p<0.001 versus the control group according to Repeated more ANOVA test and Kruskal-Wallis test)

Discussion

To the best of our knowledge, this study is the first to evaluate the effects of olive oil and flaxseed oil, alone and in combination on burn patients. Traditionally, serum albumin level has considered a nutrition indicator and a wound healing marker. Serum albumin level is influencing by non-nutritional factors, such as inflammation and hydration. Moreover, the severity of wound alone is associated with the changes in the level of albumin [30]. Our findings showed that using of olive oil could significantly increase albumin level. Also, albumin elevation was evident in the oil mixture group. On the other hand, some studies have not confirmed the effect of olive oil on albumin level [31].

Our results indicated that flaxseed oil alone did not have any significant effects on the improvement of albumin level, whereas another study from Iran showed that the oral consumption of flaxseed oil by burn patients could significantly increase the albumin level, compared to the control group [19]. Animal studies indicate that addition of flaxseed oil to the diet of mice can be effective in improving the serum albumin status [32], which is in contradiction to our findings. A study by Iizaka demonstrated that the high level of albumin was only associated with the healing of superficial wounds in patients with acute burns, and it was not predictive of wound healing in chronic cases [30].

It is known that hypoalbuminemia is a result of inflammation, malnutrition, and burns [33-35], and the increased level of albumin, as a negative acute-phase protein and a nutrition marker can predict wound healing [19]. It should be noted that increasing of albumin level in burn patients must be controlled by physicians. In the present study, treatment of albumin increase was consistently similar for all participating patients.

CRP is an inflammatory-phase protein and a non-specific marker of inflammation [36, 37], which is correlated with the severity and depth of burns [15]. Previous investigations showed that CRP reduction is associated with wound healing [19]. This marker is expected to increase during inflammation, and its reduction in wound healing and inflammatory markers can predict the burn outcomes [38]. Moreover, ferritin as an acute inflammatory-phase protein [36], is suggested as a predictor of burn outcomes that can differentiate burn survivors from non-survivors [19]. The results of our study showed that flaxseed oil in combination with olive oil had the most significant effects on reducing the levels of CRP and ferritin. However, it should be noted that using of a single herbal oil was effective to decrease these markers and was significantly different from the control group.

Olive oil is rich in antioxidant phenolic compounds, and its hydrophilic extracts contain many phenolic compounds, including simple phenols, lignans, and secoiridoids with antioxidant properties [39, 40]; it also exerts positive effects on the wound healing process [41]. In this regard, a systematic review revealed that oral use of olive oil could improve inflammatory parameters (e.g., significant reduction of CRP) [42]. In addition, flaxseed oil is rich in linoleic and alpha-linolenic fatty acids. Researchers have reported the effects of flaxseed oil on wound healing [43], and some studies have shown that ferritin and hs-CRP significantly decreased in the flaxseed oil group, compared to the control group [11, 44].

On the other hand, some studies have reported that oral intake of omega-3 compounds does not have any significant effects on CRP [10]. Ren *et al*., suggested that there is no evidence of the flaxseed effect and its compounds on hs-CRP in disagreement with a systematic theoretical study; they only reported a reduction in this marker among obese patients [45]. In this regard, another meta-analysis evaluated the effects of these compounds on CRP reduction [46]. Based on their results and our findings, it can be suggested that combination of olive oil and flaxseed oil, which are rich in omega-6, omega-9, and omega-3, could decrease the rate of inflammation by reducing CRP.

Our findings showed no significant difference in wound size in the first week of intervention. During the interval between the second and third week of intervention wound size decreased in the OF group, and this reduction was significant in the four groups (p=0.7). The results of our study showed that consumption of flaxseed oil alone, as a source of omega-3, did not have any significant effects on the size of wounds and could be only effective in combination with olive oil, which is rich in omega-6. However, Soleimani study (by evaluating the effect of oral consumption of flaxseed oil on diabetic ulcers) suggested that the size of wound (length, width, and depth) decreased significantly in the flaxseed oil group compared to the control group [11]. Babajafari Analysis of wounds showed that the flaxseed group experienced better healing than the control group on the 22nd and 25th days [19]. Also, the results reported by Najmi showed a relative reduction in the number of days of wound healing in the olive oil group, compared to the control group [31]. In this regard, a study by Gumus showed that using of olive oil accelerated wound healing and duration of wound healing in the intervention group was shorter than the control group [29].

Olive oil can be effective in reducing cholesterol, triglycerides and LDL, and when combined with flaxseed oil would result in increasing HDL. In particular Bahrul Uloomi *et al*., state that olive oil reduces triglycerides and cholesterol and improves HDL levels [47]. Carnevale *et al*., also confirm this fact that oral consumption of olive oil reduces LDL and improves HDL levels [48]. Olive oil is more effective than flaxseed oil in improving the blood lipid profile of patients, and flaxseed oil alone has no effect on reducing triglycerides and even increases cholesterol. Changes in cholesterol, triglyceride, HDL and LDL are evident after consuming flaxseed oil. Kontogianni *et al*., reported that although flaxseed oil does not have significant effects on HDL and LDL, it has a better effect on cholesterol and triglycerides. The study was conducted on 53 healthy people [49]. Few studies have been performed in the effect of vegetable oils on the lipid profile, and for more detailed investigations, it is interesting to conduct more studies in this field.

Native vegetable olive oil from Northern Iran contains large amounts of oleic and phenolic acids and is one of the important components of the Mediterranean diet. Also, flaxseed, as a traditional source of lignin is effective in diminishing skin inflammation and seems to improve the side effects of burns. Therefore, further studies need to help and determine the effects of these oils with more specific inflammatory markers. In conclusion, the results of this study showed that nutritional support with olive oil and flaxseed oil could help reducing inflammation and wound healing.

Limitations

This study was performed in a single burn specific referral center with limited numbers of participants.

Due to the limited financial conditions, tests of specific inflammatory factors such as Interleukin-6 have not been performed. Long term follow up was not considered.

Declarations

Ethics approval and consent to participate: This study approved by ethics committee of Guilan University of Medical Sciences with the code number of IR.GUMS.REC.1395.501. All patients provided written informed consents and all procedures were in accordance with the tenants of the Declaration of Helsinki and its later amendments

Consent for publication: None of the authors declared

Conflict of interest: Each author has made substantial contributions to the conception and design of the study or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. Each author has seen and approved the contents of the submitted manuscript. None of the authors has any personal or financial conflicts of interest.

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Author contributions: AGh and SM designed the overall study. MMR designed the patient's diet. MrM participated in the recruitment and data collection and also MrM investigated wound healing. EK designed the web-site for the randomization to group and carried out data analysis. All authors read and approved the final manuscript

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