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Eicosapentaenoic acid decreases inflammation and improves glucose homeostasis in patients with burns: a randomized clinical trial

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Burn is accompanied by metabolic changes. The effects of fish oil on inflammatory pathways and glucose homeostasis have been reported in the previous studies. Various forms of omega-3 fatty acids affect differently the metabolic pathways. The present study was designed to investigate the effects of fish oil containing 500 mg eicosapentanoic acid (EPA) on inflammatory markers and glucose homeostasis in patients with non-severe burns. In this prospective double-blinded parallel-design randomized clinical trial, twenty-four patients with non-severe burns covering lower than 20% of total body surface area were divided into the fish oil (1.5 gr/d EPA and 600 mg/d DHA) or controls (1.5 gr/d corn oil and 600 mg/d DHA) for three weeks. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting blood sugar (FBS), albumin, pre-albumin (PAB), transferrin, and insulin concentration were measured at baseline and end. The homeostatic model assessment for insulin resistance (HOMA-IR) was computed. The duration of hospital stay was assessed as the secondary outcome. The reduction in serum ESR and CRP levels was significantly higher in the fish oil group than the controls ($p < 0.001$). Moreover, serum fasting insulin significantly decreased in the fish oil group ($p < 0.001$). Insulin sensitivity significantly improved in the fish oil compared to the controls ($p = 0.001$). The duration of hospital stay showed no significant difference between the two groups. The most enormous clinically significant effect was observed on serum levels of FBS and insulin (Cohen's d = 2.7 and 1.4), respectively. Fish oil supplements containing 500 mg EPA improved glucose homeostasis and decreased inflammation in patients with non-severe burns. Results are not generalizable due to the small sample size. More clinical trials are needed to achieve conclusive.

Keywords Non-severe burns, Inflammation, Insulin resistance, Eicosapentanoic acid, Fish oil

Background

Burn, as a type of trauma, is recognized among the most severe physiologic stresses accompanied by metabolic alterations, including inflammation, oxidative.

stress, and insulin resistance[1]. Based on the recent literature, previous classifications of burns were not data-driven and were outdated. The current classification has been considered the burn covering ≥ 20% total body surface area (TBSA) as severe and < 20% TBSA as non-severe[2]. Despite a significant reduction in post-burn mortality over the recent decades, morbidities are still a serious clinical challenge[3]. Depending on the severity of burns, inflammatory mediators lead to hyper-metabolic situations for weeks after injury, which contribute to malnutrition[3]. Moreover, glucose intolerance and insulin resistance may occur due to the endoplasmic stress in muscles, skin, and adipose tissue[4,5]. On the other hand, proteolysis, lipolysis, and gluconeogenesis trigger systemic inflammation[1]. Energy production becomes dependent on the anaerobic pathways[6]. Hyperglycemia increases the patient's susceptibility to infection, which leads to delay in wound healing, high risk of sepsis, organ

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failure and other co-morbidities[7]. Therefore, finding a dietary component to alleviate these complications has been encouraged.

Long-chain omega-3 fatty acids are essential dietary components with anti-inflammatory, anti-arrhythmic, and immune-modulatory effects[8]. These fatty acids, both vegetable and animal sources, have a carbon-carbon double bonds located on three carbons from the methyl end of the chain. There are several forms of omega-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Any type of these fatty acids impacts differently on various metabolic pathways in the body[9].

Omega-3 fatty acids produce anti-inflammatory metabolites under the influence of cyclooxygenase and lipoxygenase enzymes. A recent systematic review and meta-analysis on seven clinical trials did not find a beneficial effect of omega-3 to reduce some complications, mortality and length of hospital stay in patients with burns[10]. This ineffectiveness could be due to various doses and types of supplements, which were used in the different degrees of burns. The published studies showed a very high heterogeneity, which draw a definitive conclusion. Therefore, we assessed the effect of EPA-rich fish oil supplement on serum inflammatory markers and glucose homeostasis in patients with non-severe burns. The duration of hospital stay was evaluated as the secondary outcome.

Methods

Study design and participants

In the present double-blinded parallel-design randomized controlled clinical trial (RCT), twenty-four patients with non-severe burns were participated. At the beginning of the study, all aims were explained to patients and an informed consent form was obtained. All procedure were performed according to the CONSORT clinical trial guidelines and Helsinki guideline for human studies. Burn severity was defined based on the current literature on the American Burn Association National Burn Research Dataset[2]. Patients with burns covering < 20% TBSA, aged 18–65 yrs, Glasgow coma scale (GCS) more than 14 who were able to obtain > 90% of their daily calorie requirements per oral (PO) were participated. Patients with a history of diabetes mellitus, organ failure, cancer, immune disorders, body mass index (BMI) lower than 18.5 or more than 30 kg/m^2, pregnant, lactating and post-menopausal women, those who needed intensive medical care, and enteral or parenteral support were excluded. Intubated patients were excluded. Patients with an allergy to fish or omega-3 supplements were omitted. Patients with burns covering ≥ 20% TBSA were omitted. All patients received the standard medical care during the study period. The study protocol has been approved by the institutional Ethic Committee of Zanjan University of Medical Sciences (Ethic code: IR. ZUMS.REC.1402.163) and registered on the Iranian registry of clinical trials on 29/11/2023 (IRCT: IRCT20231031059911N1). All procedures and methods were performed in accordance with the Helsinki guidelines for human studies.

Diet, supplementation and outcomes

Patients with burns covering < 20% TBSA were randomly assigned into receive EPA-rich fish oil (n = 16) and placebo (n = 16). The randomization unit was person and the block randomization method was used to categorize patients using allocation software, with two participants in each block. Random coded envelops were used for covering the grouping. The researcher who evaluated outcomes and patients were blinded about grouping. Participants in the groups were matched in terms of nutritional screening score which was determined by the nutritional risk assessment (NRS-2002) questionnaire at the baseline based on the assessment of nutritional status, patient's age and disease severity (Table 1). The NRS-2002 is a valid, feasible and reliable nutritional screening tool for assessing the risk of malnutrition in hospitalized adults[11]. This tool was used to match participants in terms of initial nutritional status for the study entry.

The study was started 48 h after hospitalization, and all participants were inpatient. The rule of nine was used to categorize the burn percent. At first, total daily calorie and protein requirements were computed by an expert dietitian. The Curie formula was used to compute the energy requirements as below; 24 kcal × usual body weight (kg) + 40 kcal × (TBSA) burned.

Impaired nutritional status		Severity of disease (= increase in requirements)	
Absent Score 0	Normal nutritional requirements	Absent Score 0	Normal nutritional requirements
Mild Score 1	Weight loss > 5% in 3 months or food intake < 50–75% of normal need in the preceding week	Mild Score 1	Hip fracture, chronic patients: cirrhosis, chronic obstructive pulmonary disease, chronic hemodialysis, diabetes, and oncology
Moderate Score 2	Weight loss > 5% in 2 months or BMI 18.5–20.5 kg/m^2 + impaired general conditions or food intake 20–60% of normal need in the preceding week	Moderate Score 2	Major abdominal surgery, stroke, sever pneumonia, hematologic malignancy
Severe Score 3	Weight loss > 5% in 1 month (> 15% in 3 months) or BMI < 18.5 kg/m^2 + impaired general conditions or food intake 0–25% of normal need in the preceding week	Severe Score 3	Head injury, bone marrow transplantation, intensive care patients (APACHE*>10) * Acute Physiology And Chronic Health Evaluation
Age	If ≥ 70 yrs.: 1 point s added to the total score		

Table 1. Nutritional risk screening tool-2002. Interpretation: Score ≥ 3: nutritionally at risk and nutritional care plan must initiated. Score < 3: weekly re-screening. If patients need a major operation, a preventive nutritional care plan must be considered.

The computed calorie were divided into macronutrients as follow; 20%, 50% and 30% from protein, carbohydrates and fats, respectively. The nutritionist computed the calorie and protein requirements at the baseline and these amounts advised throughout of the study. The intervention group received three times a day (Karen Co, Iran) with meals. Each fish oil capsule contained 500 mg EPA, 200 mg DHA, gelatin, glycerin, purified water and the permitted edible flavorings. Placebo capsules; similar in color, smell, odor and size were prepared by the same company, containing compounds similar to the supplements, which 500 mg corn oil used instead of EPA, 200 mg DHA, gelatin, glycerin, purified water and the permitted edible flavorings. Placebo was used as the same with supplements; with meals, three times a day. Interventions were carried out for three weeks. Fasting blood samples were collected to measure serum glucose, insulin, ESR, and CRP levels, as well as albumin, pre-albumin (PAB) and transferrin at the beginning and end of the study. HOMA-IR was computed based on the following formula:

$$HOMA - IR = [fasting\,insulin\,(mU/L) \times fasting\,glucose\,(mg/dl)]\,/405.$$

The duration of hospitalization were recorded for patients. The flow diagram of RCT has been shown in Fig. 1.

All participants were discharged from the hospital within 10 days of the start of the study. Therefore, the researcher called at the end of each week to assess the discharged patient's compliance with the prescribed diets and the delivered supplements. Moreover, in-person meeting at the end were planned to assess the patient's compliance. Patients were asked to deliver the supplements to the researcher at the end of the study. Patient's adherence to the prescribed diets and supplements were assessed by a 24 h recall which validated by the food diary and counting remaining number of delivered supplements in the container, respectively. Patients with compliance of more than 80% (for both diets and supplements) were considered in the final analysis. To achieve masking to prevent bias, the participants and care providers were unaware of which group they were enrolled in. Furthermore, the clinician's roles were limited to recruiting the patients, informing the patients about the study and then randomly assigning the patients in a 1:1 ratio to group A or B. The intervention assignment was designed by computer-generated random numbers and sealed opaque cans.

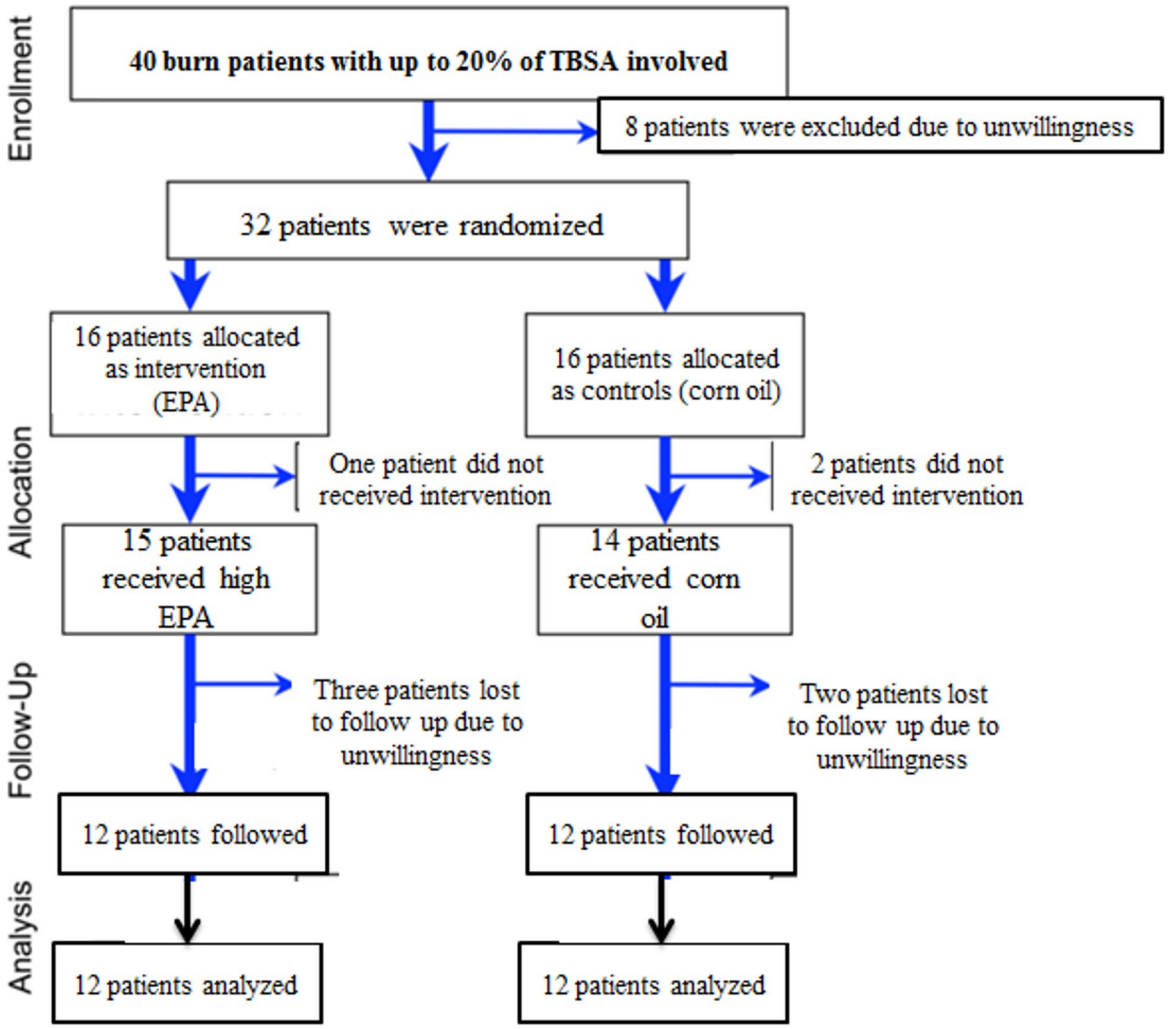

Fig. 1. CONSORT diagram of the study.

The study was terminated if the side effects including increase in PT and PTT, bleeding during the study period, and the subjects drop out for other reasons.

Sample size and statistical analysis

The sample size, considering the probability of a type 1 error equal to 5% and a power of 80%, based on a previous study[12] was computed twelve patients in each group. The below formula was used to compute the sample size in each group, which p1 = 50.4 and p2 = 21.2 about insulin variation between the two groups.

$$n_1 = n_2 = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(P_1\left(1-P_1\right) + P_2(1-P_2)\right)}{\left(P_1 - P_2\right)^2}$$

Considering 20% drop out, thirty-two patients (sixteen patients in each group) were gathered. The N4 software was used for dietary data analysis. The SPSS, version 18, was used for final statistical analysis. The quantitative and qualitative variables have been reported as means ± SE (standard error) and frequencies (percentages), respectively. In the normally distributed data, an independent sample t-test was used to compare between-group differences. In non-normally distributed data, the Mann-Whitney test was used. The paired sample t-test assessed the differences in variables, pre- and post-intervention. A Linear regression model was used to adjust the effects of baseline variables on outcomes.

Results

The baseline characteristics of participants have been shown in Table 2. All participants with non-severe burns (< 20% TBSA) participated. The burn percentage showed a statistically significant difference between the two studied groups. However, this difference was not clinically significant. The sex distribution of participants showed no significant difference between the two groups. Age, BMI, severity of malnutrition, and dietary intake showed no significant difference between the two groups before enrollment. The baseline biochemical parameters including serum FBS, insulin, HOMA-IR, albumin, PAB, transferrin, ESR, and CRP showed no significant difference at the baseline between the two groups.

All variables were assessed three weeks after supplementation (Table 3). Serum albumin was significantly higher in the EPA-rich fish oil group than the controls ($p = 0.03$), however this difference was not clinically

Variables Groups	EPA ($N = 12$) Means ± SE	Controls ($N = 12$) Means ± SE	P value†
Age, yrs.	38.7 ± 3.6	35.7 ± 4.6	0.6
Sex Male Female	9 (75%) 3 (25%)	10 (83%) 2 (17%)	0.79
BMI	26.1 ± 0.56	25.7 ± 0.57	0.56
Burn percent, %	13.3 ± 0.99	8 ± 1.08	**0.002**
Malnutrition severity			
0	6 (50%)	7(58%)	0.8
1	6 (50%)	5(42%)	
Calorie, kcal/day	2533.3 ± 43.6	2502.8 ± 39.2	0.6
Protein, g/day	67.4 ± 4.7	61.8 ± 7.4	0.4
Carbohydrate, g/day	347.1 ± 12.4	365.4 ± 13.7	0.75
Fat, g/day	97.3 ± 2.8	88.4 ± 1.5	0.09
SFAs, g/day	49.3 ± 2.2	41.3 ± 1.8	0.59
Trans-FAs, g/day	1 ± 0.01	1.2 ± 0.02	0.48
MUFAs, g/day	31.5 ± 0.8	34.3 ± 0.14	0.35
PUFAs, g/day	15.1 ± 1.1	14.7 ± 1.4	0.76
Albumin, g/dl	3.55 ± 0.19	3.6 ± 0.24	0.92
PAB, mg/dl	18.7 ± 1.3	17.9 ± 1.2	0.65
Transferrin, mg/dl	248.4 ± 15.4	239.2 ± 14.1	0.67
ESR, mm/h	19.3 ± 2	20.4 ± 1.75	0.7
CRP, mg/dl	10.25 ± 0.96	11.3 ± 1.44	0.54
FBS, mg/dl	98 ± 6.2	116.5 ± 11.27	0.54
Insulin, mU/L	60.3 ± 4.1	66.2 ± 3.4	0.29
HOMA-IR, unit	15.04 ± 1.96	19.5 ± 2.7	0.19

Table 2. Baseline characteristics of participants. †Assessed by Independent sample t–test; EPA: eicosapentanoic acid–rich fish oil; SFA: saturated fatty acid; FA: fatty acid; MUFA: mono–unsaturated fatty acid; PUFA: poly–unsaturated fatty acid; PAB: pre–albumin; ESR: erythrocyte sedimentation rate; CRP: C–reactive protein; FBS: fasting blood sugar; HOMA–IR: Homeostatic Model Assessment for Insulin Resistance; Bold values are significant.

Variables Groups	EPA ($N=12$) Means ± SE	Controls ($N=12$) Means ± SE	p value†
Calorie, kcal/day	2702.9 ± 93.6	2682.2 ± 149.2	0.8
Protein, g/day	135.1 ± 4.7	134.1 ± 7.4	0.9
Carbohydrate, g/day	357.9 ± 12.4	355.4 ± 19.7	0.9
Fat, g/day	72.1 ± 1.8	78.4 ± 3.5	0.7
SFAs, g/day	19.3 ± 2.2	21 ± 1.8	0.59
Trans-FAs, g/day	0.09 ± 0.001	0.12 ± 0.01	0.48
MUFAs, g/day	32.4 ± 0.8	33.3 ± 0.6	0.35
PUFAs, g/day	20.1 ± 1.1	21.7 ± 1.4	0.76
Albumin, g/dl	3.76 ± 0.19	3.2 ± 0.17	**0.03**
PAB, mg/dl	21.04 ± 1.7	15.1 ± 1.5	**0.02**
Transferrin, mg/dl	250.4 ± 23.5	210.5 ± 20.3	0.22
ESR, mm/h	9.5 ± 1.6	20.9 ± 1.9	< **0.001**
CRP, mg/dl	3.9 ± 0.73	11.8 ± 1.3	< **0.001**
FBS, mg/dl	88 ± 2.01	113.7 ± 9.7	**0.01**
Insulin, mU/L	26.1 ± 4.2	62.3 ± 5.1	< **0.001**
HOMA-IR, units	5.9 ± 1.09	18.2 ± 3.3	**0.001**
Hospital stay, day	6.4 ± 0.43	9.1 ± 0.78	**0.005**

Table 3. Biochemical and dietary parameters after three weeks in the studied groups. †Assessed by Independent sample t–test ; EPA: eicosapentanoic acid–rich fish oil; PAB: pre–albumin; ESR: erythrocyte sedimentation rate; CRP: C–reactive protein; FBS: fasting blood sugar; HOMA–IR: Homeostatic Model Assessment for Insulin Resistance; Bold values are significant.

Variable group	EPA ($N=12$) Means ± SE	Control ($N=12$) Means ± SE	p value†	Cohen's d
Diff Alb, g/dl	0.2 ± 0.08	− 0.42 ± 0.08	< **0.001**	0.006
Diff PAB, mg/dl	2.3 ± 0.92	− 2.8 ± 0.52	< **0.001**	0.02
Diff transferrin, mg/dl	1.9 ± 14.8	− 28.7 ± 7.2	0.09	1.2
Diff FBS, mg/dl	− 10 ± 5.4	− 2.8 ± 2.03	0.27	2.7
Diff insulin, mU/L	− 34.2 ± 3.7	− 4.01 ± 3.3	< **0.001**	1.4
Diff HOMA, units	− 9.2 ± 1.7	− 1.3 ± 1.05	**0.001**	0.3
Diff ESR, mm/h	− 9.8 ± 1.7	0.5 ± 0.8	< **0.001**	0.3
Diff CRP, mg/dl	− 6.3 ± 1.07	0.5 ± 0.79	< **0.001**	0.5

Table 4. Mean changes of the assessed parameters from the baseline up to the end. †Assessed by Independent sample t–test; EPA: eicosapentanoic acid–rich fish oil; PAB: pre–albumin; ESR: erythrocyte sedimentation rate; CRP: C–reactive protein; FBS: fasting blood sugar; HOMA–IR: Homeostatic Model Assessment for Insulin Resistance; Bold values are significant. Cohen's d presents the effect size of supplementation on each parameter, where up to 0.2: small, 0.2–0.5: moderate, and >0.8 are related to big effect sizes

significant. Serum pre-albumin level showed a statistically significant difference between the two groups ($p=0.02$). Serum ESR and CRP levels significantly decreased in the EPA-rich fish oil ($p<0.001$). Moreover, serum FBS and insulin levels significantly decreased in the EPA-rich fish oil ($p=0.01$ and $p<0.001$, respectively). Insulin resistance (HOMA-IR) significantly decreased in the EPA-rich fish oil than the controls ($p=0.001$). The controls were hospitalized for a more extended time compared to the EPA-rich fish oil ($p=0.005$).

The mean difference of the assessed parameters has been shown in Table 4. As shown, ESR (-9.8 ± 1.7 vs. 0.5 ± 0.8 mm/hr), and CRP (-6.3 ± 1.07 vs. 0.5 ± 0.79 mg/dl) levels significantly decreased in the EPA-rich fish oil, however these markers increased in the controls ($p<0.001$ and $p<0.001$, respectively). Serum insulin significantly decreased in the EPA-rich fish oil than the controls (-34.2 ± 3.7 vs. -4.01 ± 3.3, $p<0.001$), after three weeks. Moreover, the HOMA-IR significantly decreased in the EPA-rich fish oil than the controls (-9.2 ± 1.7 vs. -1.3 ± 1.05, $p=0.001$). Serum level of albumin and PAB significantly decreased in the controls, however increased in the EPA-rich fish oil ($p<0.001$ and $p<0.001$, respectively). To determine the clinical relevance of findings, we used Cohen's d to compute the effect sizes. As shown in Table 4, big effect sizes were observed on serum FBS, insulin and transferrin levels. However, the effect size of supplementation was moderate for HOMA-IR and serum levels of CRP. Others including serum levels of Alb and PAB showed small effect sizes.

Adjusting for the baseline parameters, including sex, age, percent of burns and dietary intake, the serum ESR (mean difference = 0.73, 95%CI = 5.5–15.1, $p<0.001$) and CRP (mean difference = 0.72, 95%CI = 3.6–9.7, $p<0.001$) levels showed a significant difference between the two studied groups. The decrease in serum fasting

insulin was 24% higher in the EPA-rich fish oil than the controls (95%CI = 18.7–38.9, $p < 0.001$). Insulin sensitivity improved in the EPA-rich fish oil than the controls (mean difference = 3.8, 95% CI = 3.3–11.5, $p = 0.001$).

Discussion

For the first time, a small sample size clinical trial was designed to evaluate the effects of EPA-rich fish oil supplement on some inflammatory markers and glucose homeostasis in patients with non-severe burns. The hospital stay was also assessed. Following, results have been discussed categorically. Herein, the moderate effect size of EPA-rich fish oil supplementation was observed on serum levels of inflammatory markers at the clinical relevance. The anti-inflammatory effects of omega-3 have been approved in the previous clinical trials[13–16]. However, no study was founded on human subjects about the effects of EPA-rich fish oil supplement on markers of inflammation. Our study showed the beneficial effects of EPA-rich fish oil on inflammatory markers. Albumin and PAB significantly increased in the EPA-rich fish oil, three weeks after burns, but the mean changes of these markers were not clinically significant in the controls. Burns are one of the most common forms of trauma that impose significant socio-economic and psychological costs on both the healthcare system and patients[1,17]. A recent RCT assessed the anti-inflammatory effects of flaxseed (a source of omega-3 fatty acids) compared with olive oil (a source of omega-9 fatty acids) in wound healing of patients with severe burns. Patients with burns covering 20–45% TBSA categorized to four groups, including olive oil, flaxseed oil, olive and flaxseed oil, and controls (received salad). The most significant reduction was observed in CRP and ferritin levels in the olive plus flaxseed oil, while the lowest reduction was seen in the control group. Compared to the controls, olive oil significantly increased serum albumin. A significant improvement in wound healing was observed at the end of the second and third weeks in the olive plus flaxseed oil[18]. Our results are following with this study regarding serum albumin level. Serum albumin and PAB were significantly increased in the EPA-rich fish oil group after three weeks but decreased in the controls. Albumin and PAB are negative phase reactant proteins with a half-life of 14–20 and 2–3 days, respectively that are produced by liver. Both of them are negative inflammatory proteins, which decrease in trauma and inflammation[19]. In our study, the mean changes of serum PAB were significantly higher in the EPA-rich fish oil than the controls, which may be related to improve in inflammatory status of patients. In a three-week, double blind RCT on patients with burns covering 20–45% TBSA, serum CRP levels were significantly lower in omega-3 supplemented group compared to the controls[12]. Moreover, the mean changes of CRP were significantly higher in this group than the controls. Our results agree with the mentioned study. The mean serum CRP and ESR levels were significantly different between the EPA-rich fish oil and the controls, adjusted for the baseline variables. In a crossover study, the effects of 10-week supplementation with EPA-only and DHA-only (3 g/d) were assessed on fasting serum metabolites in 21 subjects (9 men and 12 post-menopausal women) with chronic inflammation. Results indicated that the EPA and DHA exhibit common and differential effects on cell metabolism in subjects with chronic inflammation and some key aspects of metabolic syndrome[20]. In a recent animal study, EPA lowered murine fat mass accumulation, reversed the effects of a high-fat diet on circulating levels of some of the inflammatory/metabolic markers[21]. The clinical relevance of our findings showed the big effect size of EPA-rich fish oil on serum levels of FBS and insulin in the patients with non-severe burns. The hypermetabolic state increases the rate of gluconeogenesis, proteolysis and lipolysis in the body due to the secretion of stress hormones, including catecholamines (epinephrine, norepinephrine and dopamine), and cortisol, which finally increases the blood sugar and induces resistance to insulin in muscle and fat tissue[22,23]. Based on the European nutritional guidelines, immunonutrition containing omega-3 fatty acids, glutamine, arginine, nucleotides, and antioxidants have a positive effect on the duration of hospitalization, the occurrence of infectious events, and morbidity[24]. The results of previous studies in other countries cannot be generalized due to differences in the age of participants, duration of supplementation, type of supplements (omega-3 formula or omega-3 supplement), and type of omega-3 (fish oil or vegetable oils). Different care systems in different countries also contribute to these inconsistencies. In a three-week RCT on patients with burns covering 20–45% TBSA, insulin and HOMA-IR seemed clinically lower, but not statistically, in the omega-3 group compared to the controls[12]. Our results showed a significant difference between the EPA-rich fish oil and the controls, both clinically and statistically in terms of serum insulin and HOMA-IR. Serum insulin and HOMA-IR significantly decreased in the EPA-rich fish oil after three weeks, but serum FBS showed no significant difference that is inconsistent with the mentioned study. In a crossover study[20], the effects of 10-week supplementation with EPA-only and DHA-only (3 g/d) were assessed on fasting serum metabolites in 21 subjects (9 men and 12 post-menopausal women) with chronic inflammation. Results indicated that EPA and DHA exhibit both common and differential effects on circulating levels of insulin and glucose. The effects of omega-3 supplementation on the hospital stay showed various results in the previous studies[25–31]. In the present study, the duration of hospital stay was significantly higher in the controls than the EPA-rich fish oil; however it was not significant in the adjusted model. In a primary RCT on acute thermal burn patients covering 10–89% TBSA on the modular tube feeding containing protein (87% whey, 9% arginine, 2% cysteine, 2% histidine), carbohydrate (maltodextrin), fat (50% fish oil, 50% safflower oil): 5 g omega-3 FA in 1029.80 g of diet for five weeks, a significant reduction was seen in the duration of hospital stay in the fish oil supplemented group[25]. In another primary RCT on 49 acute burn patients covering 2.5–82.5% TBSA, the enteral nutrition containing fish oil showed no significant effect on the duration of hospital stay compared to the controls for two weeks[26]. As seen, these studies are ancient and primitive with inconsistent results, which may be associated with the heterogeneity in the severity of included patients, doses and types of omega-3. As previously mentioned, studies on patients with burns are very scarce and primitive. In a cohort study on 661 patients with different diagnoses, omega-3 reduced the length of hospital stay in patients on total parenteral nutrition[27]. Results are not comparable with our study because subjects on the PO were included in the present study. Moreover, patients in the mentioned study are very heterogenic on the diagnoses, which affect the outcomes. Studies on the effects of oral administration of omega-3 (2–3 gr/day) on the hospital stay in patients undergoing coronary artery bypass graft surgery showed

inconclusive results[28–31]. As shown, different characteristics of the studied patients, the dose of supplement, the duration and form of supplementation, and even different care-treatment systems in different countries provide different results. Some pathways are suggested for the effects of EPA on inflammation, and glucose homeostasis by alterations in the gut microbiome[32–35]. Studies about the effects of EPA on the gut microbiome are very innovative and there is a need to focus on this area by conducting further studies.

The present small sample size study is the first single-centre clinical trial on patients with non-severe burns, based on the new classification, to assess the effect of EPA-rich fish oil supplementation on inflammatory markers and glucose homeostasis. Severity of malnutrition was matched between the intervention and controls, which was not considered in the previous studies. Calorie and protein intake were computed for each participant and a prescribed personalized diet was delivered to omit the effects of differences in dietary intake on the assessed markers. However, the patient's adherence to the prescribed diet was a primary challenge. Based on the Burn Unit Nutritional Support recommendation, the nutritional support should be initiated for the following patients: ≥20% TBSA burns, all intubated patients, any patient who cannot meet their nutritional needs with orally and patients who arrive with pre-existing malnutrition[37]. Our inclusion criteria were burns with < 20% TBSA, who were not ventilator-dependent. Malnutrition was matched between the two groups and patients with severe malnutrition did not include. These notes were considered to omit confounding factors such as the baseline nutritional status or type of dietary support, which may effect on the outcome. Obese patients were excluded due to the baseline chronic inflammatory status in the body, which affect the healing process. Our study had a more homogeneous participant pool. However, similar to other studies, there are some limitations. Low sample size is the most important of them. Clinical trials in patients with burns are complex and cooperation of patients is low. It would be proposed to compute total daily calorie and protein requirements in "kcal/kg/day" and "g/kg/day", respectively to represent the adequacy of needs, not over nutrition. It is noted that daily calorie and protein requirements were computed only at the baseline and did not adjusted throughout of the hospital stay based on unintentional weight loss or inadequate wound healing. Results of the present study are not generalizable to other patients because of single-centre design. Moreover, clinical care systems are different is various countries that make it difficult for generalize the results. More studies with a larger sample size are needed. Moreover, comparing the effect of EPA with DHA is suggested for the future. Evaluating the effects of EPA or DHA in patients with moderate or severe burns is also proposed. Assessing the microbiome alterations in patients with burns, before and after the injury opens new windows towards identifying pathways controlling inflammation and glucose homeostasis. More clinical trials in multi-centers are needed to reach a concise result. It is suggested that wound healing, infection rate and patient's re-admission should be assessed in future studies.

Conclusions

EPA-rich fish oil supplementation in a dose of 1.5 gr per day for three weeks decreased inflammation, improved glucose homeostasis in patients with non-severe burns. The most enormous clinically effect size was observed on serum FBS and insulin levels. Results are not generalizable due to the small sample size. More clinical trials are needed to achieve conclusive.

Future studies are needed in multi-centre design with a larger sample sizes to confirm these result.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

All authors have contributed to the development of this study research. M.A.M participated in the data collection, wrote the first draft of this manuscript and subsequent versions, and approved the version as submitted. S.N.M and A.Sh participated in the conceptualization of this research project, supervised the study conduction, critically reviewed and commented on drafts of this manuscript, and approved the version as submitted. S.A.S conducted the data analysis, studied the version of the manuscript and approved.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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