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Flaxseed oil supplementation decreases C-reactive protein levels in chronic hemodialysis patients

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ARTICLE INFO

Article history:
Received 17 October 2011
Revised 20 July 2012
Accepted 20 August 2012

Keywords:
Hemodialysis
Inflammation
C-reactive protein
Flaxseed oil
Clinical trial
Human

ABSTRACT

Malnutrition and chronic inflammation in dialysis patients negatively impact their survival prognosis, and nutrients, such as omega-3 oils, are postulated to reduce proinflammatory response. In this randomized, double-blind, multicenter, placebo-controlled trial, we investigated the effects of flaxseed oil (FO) on the inflammatory state of patients with chronic renal failure undergoing renal replacement therapy with hemodialysis (HD). We hypothesized that FO supplementation lowers C-reactive protein (CRP) levels. One hundred sixty patients with chronic renal failure who received HD therapy of 3 dialysis units over a 3-month period in South Brazil were included. The patients received blind doses of FO (1 g twice a day) and placebo (mineral oil, 1 g twice a day) for a period of 120 days. Inflammation was observed in 89 patients (61%) at the beginning of the study. There was a correlation between CRP and the body mass index (R_s = 0.22; P = .022) and high-density lipoprotein cholesterol (R_s = –0.23; P = .032), and the CRP levels decreased significantly over time in the group that received FO compared with the control group (P < .001). During the study period, 33.3% of the FO group changed from an inflamed to a not-inflamed category, whereas only 16.9% changed in the mineral oil group (P = .04). We conclude that the administration of FO decreases the CRP levels and that inflammation in HD patients appears to be correlated to their body mass index and reduced high-density lipoprotein cholesterol levels. Studies with a larger number of patients and over a longer duration are necessary to corroborate these findings.

1. Introduction

A significant proportion of patients undergoing renal replacement therapy (RRT) with hemodialysis (HD) or peritoneal dialysis present a microinflammatory state, which is clinically detected by increased levels of C-reactive protein (CRP) and other inflammatory markers, mainly interleukin 1 and interleukin 6 [1,2]. This proinflammatory state is predictive of higher mortality levels and is associated with the malnutrition, inflammation, and atherosclerosis syndrome [3] and other factors, including the dialysis treatment itself [4–6]. Moreover, several uremic patients present a deficiency of

Abbreviations: αLNA, α-Linolenic acid; BMI, Body mass index; CRP, C-reactive protein; DHA, Docosahexaenoic; EPA, Eicosapentaenoic acid; FO, Flaxseed oil; HD, Hemodialysis; HDL, High-density lipoprotein; HDL-c, High-density lipoprotein cholesterol; IL, Interleukin; LDL, Low-density lipoprotein; MO, Mineral oil; n-3, Omega-3; n-6, Omega-6; RRT, Renal replacement therapy; TNF-α, Tumor necrosis factor α; URR, Urea reduction ration.

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0271-5317/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nutres.2012.08.007

essential fatty acids and abnormal prostaglandin synthesis that may produce or worsen the proinflammatory state [7].

Animal experiments and human clinical trials have suggested that fish oils, which contain polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) (20:5n3) and docosahexaenoic acid (DHA) (22:6n3), have anti-inflammatory properties. Some evidence includes the inhibition of proinflammatory eicosanoids derived from n-6 fatty acids, such as arachidonic fatty acid (20:4n6), and a decreased in the activity from proinflammatory cytokines [8–11]. These findings were further corroborated by Ewers et al [12] in a study in which an adult HD population supplemented with unsaturated fat showed beneficial effects in terms of weight gain and decreased levels of CRP. Bowden et al [13] obtained similar results for the CRP levels in patients supplemented with fish oil. However, the main difficulties for the clinical use of fish oil are the sensorial intolerance and the high cost, leading to a high incidence of discontinuation even before the therapeutic effects occur [14]. Other oils are described as having similar effects; nevertheless, few studies have been conducted to evaluate the action of EPA and DHA precursors, such as α-linolenic acid (αLNA), which are present in high quantities in some vegetable oils. Flaxseed oil (FO) (*Linumusitatissimum*) does not contain EPA and DHA fatty acids, but it is the only oil of plant origin known to have significant amounts of αLNA and is considered to be the seed oil with the highest concentration of this fatty acid [15]. As the concentration and proportion of the omega-3 (n-3) and omega-6 (n-6) fatty acids are considered ideal, FO has been tested in clinical trials that have described a potential beneficial effect for certain disorders, such as dyslipidemia and cardiovascular disease [16–19]. However, there are no studies that have tested FO in patients with end-stage renal disease undergoing RRT with HD.

Considering its characteristics and the lack of significant side effects as well as good acceptability, we undertook the present randomized clinical trial to test the hypothesis that therapeutic doses of FO could lead to a decrease in the CRP levels in patients undergoing RRT with HD.

2. Methods and materials

2.1. *Patients and study design*

One hundred sixty patients with terminal renal failure who were undergoing chronic HD from 3 dialysis units in the southern state of Rio Grande do Sul, Brazil, were included in a double-blind, randomized clinical trial. Informed consent was obtained by all patients. The following inclusion criteria were observed: (*a*) 18 years old; (*b*) RRT with HD for at least 90 days; (*c*) absence of known infection, active inflammation, malignancy, HIV seropositivity, and autoimmune disease; (*d*) absence of intravenous dialysis catheters; (*e*) no transplants; and (*f*) acceptance of participation.

2.2. *Methods*

The demographic variables and laboratory data included the age, sex, race, time under RRT, primary renal disease, CRP, total cholesterol and high-density lipoprotein (HDL), triglycerides, complete blood counts, calcium, phosphorus, parathyroid hormone, alanine aminotransferase, anti–hepatitis C antibodies, and hepatitis B surface antigen. The urea reduction rate, Kt/V, and calcium-phosphorus product were also calculated. C-reactive protein was measured using the CardioPhase hsCRP reagent method (Dade Behring, Marburg, Germany). Other measurements were performed using standard clinical laboratory methods.

The patients included were randomized into 2 treatment groups: a FO group, receiving 1.0 g of FO plus α-tocopherol (3.5 mg) twice a day, and the control mineral oil (MO) group, receiving 1.0 g of MO + 3.5 mg of α-tocopherol twice a day. The FO and placebo capsules were visually identical. The patients in both groups were instructed to take the capsules for 120 days; adherence was assessed by counting the remaining capsules every 30 days. The laboratory data were collected at baseline, 60, and 120 days after the beginning of therapy. The serum cholesterol and fractions and triglycerides were measured at baseline and 120 days in the 84 patients who could fast for the sampling.

The patients were considered to have inflammation if the serum CRP is 5.1 mg/L [32]. Those patients unable to tolerate intervention or who developed any of the exclusion criteria during the study were excluded. The patients were also analyzed according to intention to treat. The study was approved by the research ethics committee of the coordinating center (Hospital de Clínicas de Porto Alegre).

2.3. *Statistical analyses*

The sample size was calculated to obtain a power of 80%, α error of 5%, and 30% reduction of the CRP levels with the FO supplementation. The statistical analyses were performed using the SPSS software 16.0 version for Windows (Chicago, IL, USA). The continuous variables are shown as the means ± SD. The comparisons of the continuous variables between the groups were performed using a mixed-model analysis and an analysis of variance. The categorical variables were analyzed using the χ^2 or Fisher exact tests. The asymmetric variables were logarithmically transformed and compared using the Wilcoxon Mann-Whitney *U* test. The correlations were calculated using Pearson or Spearman correlation coefficients. $P < .05$ was considered statistically significant.

3. Results

A total of 160 patients were randomized at a 1:1 ratio to receive FO (80 patients) or MO (80 patients) for 120 days. There were 15 exclusions after the randomization and before the study's initiation. Another 31 exclusions occurred during the therapy period; thus, 114 patients completed the study. The timing and explanations for the excluded patients are shown in Fig. 1. There was no significant difference in the comparisons of the exclusion causes between the groups ($P = .34$). Among the analyzed individuals, there were 75 men (52%) and 116 whites (80%). The mean age of the subjects was 59.3 ± 12.8 years, and the mean body mass index (BMI) values were 25.6 ± 3.2. The demographic and laboratory data were analyzed at the