NUTRITION RESEARCH 32 (2012) 921–927

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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 
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 $\chi^2$ 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

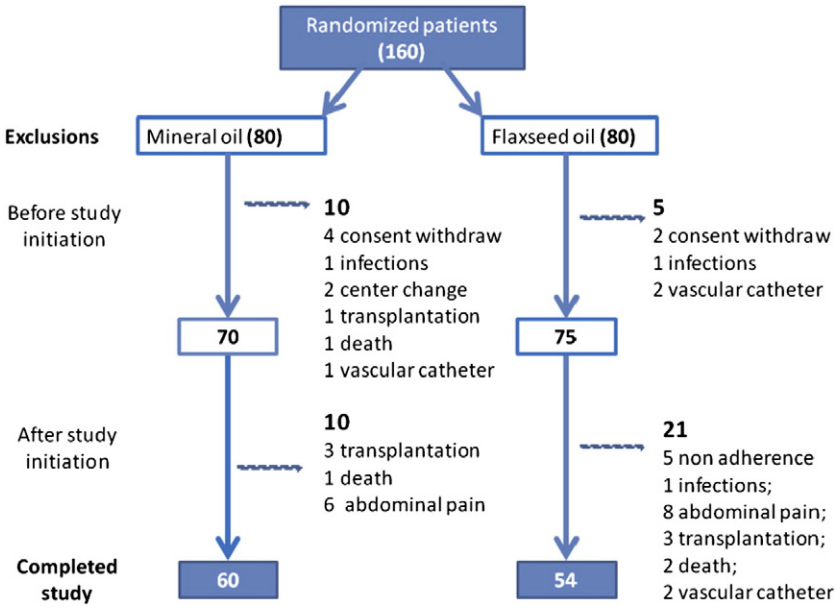


**Fig. 1 – Numbers of patients in each phase of the study and respective causes for exclusion.**

beginning of the study according to the randomization group (Table 1); the group of patients randomized for the FO group presented significantly higher CRP values ($P = .014$) and significantly lower total cholesterol values ($P = .007$). The laboratory data were collected at baseline for 145 patients due to intention to treat.

In the initial analysis, inflammation was present in 89 (61%) of the 145 patients. A statistically significant correlation was found between the BMI and baseline CRP ($R_s = 0.22$; $P = .022$), whereas a negative correlation with similar strength was found between the HDL cholesterol (HDL-c) and baseline CRP levels ($R_s = –0.23$; $P = .032$).

In the FO group, the comparison between the first and the last analyses displayed a statistically significant decrease in the CRP ($P < .001$), total cholesterol ($P = .004$), and low-density lipoprotein (LDL) cholesterol ($P = .001$) values and an increase in the HDL-c ($P = .004$) values; yet, similar findings were not observed in the MO group (Table 2). Throughout the study, we observed that the CRP variation in the FO group was higher than that observed for the MO group ($P < .001$). In this interaction assessment, the decrease in the CRP values for the FO group reached a statistical significance (time 1 × time 2 and 3), whereas the values for the MO group remained stable (Fig. 2). In the mixed-model analysis, the FO group achieved a significant reduction in the CRP values when compared with the MO group ($P = .018$).

In another approach, by comparing the initially inflamed with the noninflamed groups, we observed lower urea reduction ration (URR) and Kt/V ("dialysis dose") values for the inflamed group ($P < .01$). These individuals also presented a higher BMI mean ($P = .03$), but the comparisons of the other study variables did not present statistically significant differences (Table 3). Moreover, in the FO group, a decrease in the percentage of inflamed patients was observed throughout the study, falling from 36.3% to 23.9% to 21.2%, respectively, at times 1, 2, and 3 ($P = .004$). In contrast, no statistically significant differences were observed in the respective times of assessment for the MO group ($P = .487$).

A further analysis was performed by separating the effects of intervention in the inflamed and noninflamed groups. Among the noninflamed patients, neither intervention produced a significant decrease in the CRP levels (FO 1.26 ± 1.25 to 0.68 ± 1.49 and MO 2.14 ± 1.15 to 2.33 ± 1.28; P, nonsignificant). Conversely, as shown in Fig. 3, a statistically significant decrease in the CRP levels was observed in the group of inflamed patients who received FO ($P < .001$); however, the

**Table 1 – Demographics and baseline measurements in the study patients**

| Parameter | FO group (n = 70) | MO group (n = 75) | P |
|---|---|---|---|
| Male (%) | 39 (55.7) | 46 (61.3) | .694 |
| Race (% white) | 67 (95.7) | 70 (93.3) | .623 |
| Age (y) [a] | 55.7 ± 13.0 | 58.3 ± 14.8 | .338 |
| Time on HD (mo) [b] | 28.5 (14-59.5) | 34.5 (16.2-72) | .507 |
| BMI (kg/m$^2$) [a] | 25.1 ± 3.47 | 24.2 ± 4.27 | .212 |
| DM (%) | 36 (51.4) | 34 (45.3) | .220 |
| CRP (mg/L) [b] | 8.0 (2.3-16.8) | 4.4 (2.3-7.6) | .014 |
| Ht (%) [a] | 34.2 ± 4.93 | 33.8 ± 4.97 | .653 |
| Hb (g/dL) [a] | 11.2 ± 1.55 | 10.9 ± 1.57 | .494 |
| URR [a] | 70.0 ± 9.89 | 71.9 ± 6.97 | .259 |
| Kt/V [a] | 1.46 ± 0.34 | 1.55 ± 0.32 | .202 |
| Ca (mg/dL) [a] | 8.43 ±1.04 | 8.22 ± 0.92 | .220 |
| $PO_4$ (mg/dL) [b] | 5.1 (4.08-6.83) | 5.0 (3.83-7.08) | .838 |
| Cholesterol (mg/dL) [a] | 193.2 ± 58.0 | 165.9 ±46.4 | .017 |
| HDL (mg/dL) [a] | 30.8 ±7.56 | 34.4 ± 14.3 | .591 |
| LDL (mg/dL) [a] | 121 ±45.8 | 94.5 ± 32.5 | .243 |
| TG (mg/dL) [b] | 177 (128-266) | 163.5 (112-205) | .178 |

Abbreviations: DM, diabetes mellitus; HT, hematocrit; Hb, hemoglobin; Ca, calcium; $PO_4$, phosphorus; TG, triglycerides.
[a] Values at baseline are expressed as means ± SD.
[b] Values at baseline are expressed as median and range.

**Table 2 – Baseline and 120 days measurements in the study patients**

| Parameter | Baseline | 120 d | P | Baseline | 120 d | P |
|---|---|---|---|---|---|---|
| | FO group (n = 70) | | | MO group (n = 75) | | |
| CRP (mg/L) [a] | 8.1 (4.9-19.5) | 4.2 (1.7-8.5) | <.001 | 4.4 (2.4-7.5) | 3.7(1.3-9.0) | .337 |
| Ht (%) [b] | 34.2 ± 4.93 | 33.9 ± 5.7 | .705 | 33.8 ± 4.97 | 34.1 ± 5.26 | .769 |
| Hb (g/dL) [b] | 11.2 ± 1.55 | 10.9 ± 1.9 | .461 | 11.0 ± 1.57 | 10.9 ±1.62 | .951 |
| URR [b] | 70.0 ± 9.89 | 69.2 ± 8.74 | .536 | 71.9 ± 6.97 | 71.5 ± 8.91 | .608 |
| Kt/V [b] | 1.46 ± 0.34 | 1.43 ± 0.33 | .443 | 1.55 ± 0.32 | 1.47 ± 0.33 | .05 |
| Ca (mg/dL) [b] | 8.43 ± 1.04 | 8.1 ± 1.12 | .055 | 8.22 ± 0.92 | 8.43 ± 0.95 | .084 |
| $PO_4$ (mg/dL) [a] | 5.1 (4.08-6.83) | 4.8 (3.75-6.0) | .08 | 5.0 (3.83-7.08) | 4.55 (3.42-5.47) | .06 |
| Cholesterol (mg/dL) [b] | 193.2 ± 58.0 | 178.6 ± 44.4 | .004 | 165.9 ± 46.4 | 162.5 ± 40.7 | .588 |
| HDL (mg/dL) [b] | 30.8 ± 7.56 | 33.3 ± 8,79 | .004 | 34.4 ± 14.3 | 35.0 ± 15.1 | .591 |
| LDL (mg/dL) [b] | 121.0 ± 45.8 | 107.6 ± 31.7 | .001 | 94.5 ± 32.5 | 88.7 ± 35.3 | .243 |
| TG (mg/dL) [a] | 177 (128-266) | 147 (111-231) | .06 | 163.5 (112-205) | 184 (127-249) | .05 |

[a] Values are expressed as median and range.
[b] Values are expressed as means ± SD.

reduction in the CRP levels for the MO group was minimal and statistically not significant.

## 4. Discussion

In spite of the significant advances in RRT technology, particularly in regard to HD equipment and techniques, uremic patients continue to have a high mortality rate, mainly due to cardiovascular events [20–22]. The traditional risk factors for cardiovascular mortality include hypertension, congestive heart failure, dyslipidemias, diabetes, and smoking. More recently, inflammation, oxidative stress, hyperhomocysteinemia, and malnutrition have also been associated with the cardiovascular risk profile for mortality in these patients [23–25]. Furthermore, certain risk factors specifically related to uremia are currently recognized and include divalent ion disturbances, anemia, a chronic hypervolemic state, and coronary calcification [26–28]. Several studies reported that chronic inflammation has an elevated prevalence in the uremic population [29,30]. The observation that inflammation is strongly related to the atherogenic process was reported in both renal and nonrenal patients, and it was demonstrated that the inflammatory process contributes to increased morbidity and mortality in chronic HD patients [30]. The causes of inflammation in HD patients are complex and multifactorial, including blood exposure to the dialysis membranes and water, clinical or subclinical infection of the vascular access port, malnutrition, reduced levels of antioxidants, and increased oxidative stress [31].

The CRP level reflects the generation of proinflammatory cytokines, such as interleukins (ILs) 1 and 6 and tumor necrosis factor α (TNF-α), which are elevated in a significant

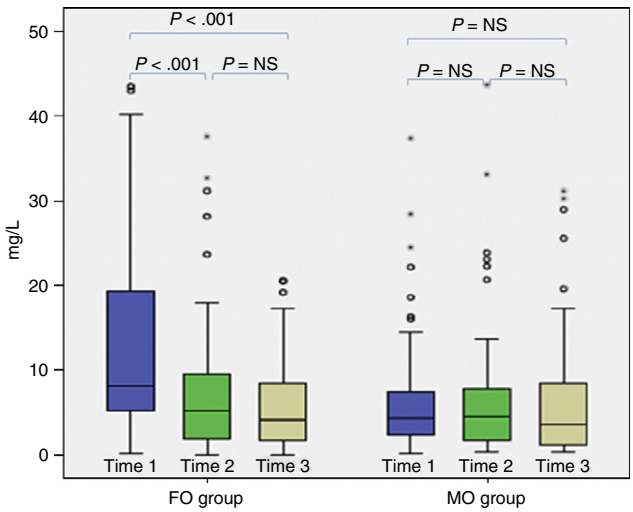


**Fig. 2 – C-reactive protein (milligrams per liter) variation at 3 time points of assessment. Box and whisker plots showing medians (horizontal line) P 25-75 (box) and P 10-90 (bars) and outliers (circles). In the FO group, the decrease in the CRP was statistically significant (CRP 1 × CRP 2 and CRP 3). In the MO group, there was no statistically significant difference in the comparisons. P 25-75 = median 25th to 75th percentile; P 10-90 = 10th to 90th percentile.**

**Table 3 – Comparison of demographics and measurements of study patients grouped as inflamed and not inflamed**

| Parameter | Inflamed (n = 89) | Not inflamed (n = 56) | P |
|---|---|---|---|
| Age (y) [a] | 57.2 ± 14.1 | 57.1 ± 14.1 | .976 |
| Time on HD (mo) [b] | 26 (13.3-71) | 37 (23-67.5) | .142 |
| White (%) | 71 (80.8) | 45 (81.7) | .141 |
| Male (%) | 48 (54.2) | 23 (42.2) | .554 |
| BMI ($kg/m^2$) [a] | 25.5 ± 3.94 | 23.3 ± 3.27 | .03 |
| CRP (mg/L) [b] | 9 (6.7-20.0) | 2.2 (1.45-3.55) | <.001 |
| Ht (%) [a] | 32.9 ± 4.78 | 34.1 ± 5.09 | .816 |
| Hb (g/dL) [a] | 11.0 ± 1.53 | 11.1 ± 1.60 | .624 |
| URR [a] | 70.0 ± 9.89 | 73.5 ± 6.62 | <.01 |
| Kt/V [a] | 1.44 ± 0.32 | 1.60 ± 0.32 | <.01 |
| Ca (mg/dL) [a] | 8.43 ± 1.04 | 8.23 ± 1.02 | .20 |
| $PO_4$ (mg/dL) [b] | 5.25 (4.2-6.88) | 4.8 (3.75-7.05) | .306 |
| Cholesterol (mg/dL) [a] | 178.0 ± 52.4 | 183.4 ± 56.7 | .653 |
| HDL (mg/dL) [a] | 31.7 ± 11.8 | 33.7 ± 10.9 | .436 |
| LDL (mg/dL) [a] | 105.9 ± 39.7 | 110.1 ± 47.2 | .662 |
| TG (mg/dL) [b] | 155 (102.5-209) | 157.5 (124.2-250.2) | .377 |

Difference in the comparisons.
[a] Values are expressed as means ± SD.
[b] Values are expressed as median and range.

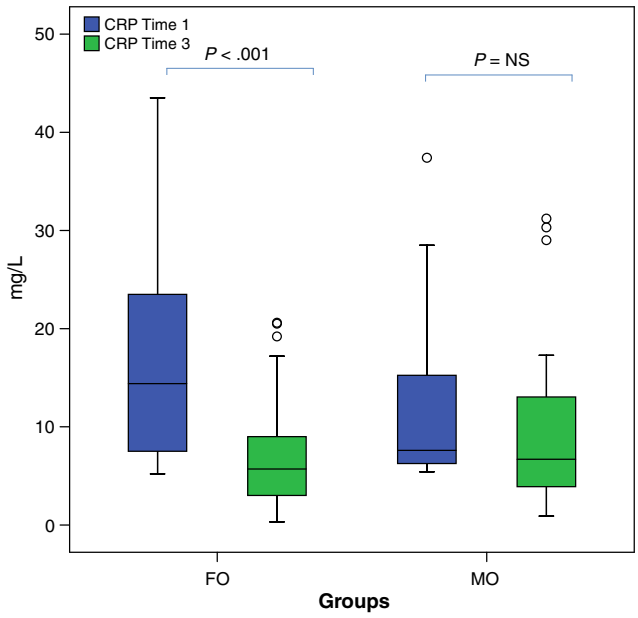


**Fig. 3 – C-reactive protein variation at the beginning and at the end of the study period. Assessment of inflamed subjects according to intervention. Box and whisker plots showing medians (horizontal line) P 25-75 (box) and P 10-90 (bars) and outliers (circles). In the FO group, the decrease in the CRP was statistically significant (P < .001). In the MO group, the reduction of CRP levels is not statistically significant. P 25-75 = median 25th to 75th percentile; P 10-90 = 10th to 90th percentile.**

portion of patients with end-stage renal disease and are considered to be predictors of mortality in this population [32]. High levels of acute-phase proteins, such as CRP, are directly linked to atherogenic properties and may intensify the accelerated atherogenesis observed in patients undergoing HD [27,33]. Perhaps the main contributors to the elevated frequency of inflammation in this population are the exposure of the blood to bioincompatible extracorporeal circuits, including the dialysis filters and lines, and exposure to nonsterile dialysis water and solutions [1].

The 2 physiologically essential and complementary fatty acids in humans are linoleic acid [18:2 (n-6)] from the n-6 family and αLNA from the n-3 family [18:3 (n-3)] [16,34,35]. In Western cultures, the effects of an inadequate intake of α-linolenic fatty acid compared with linoleic fatty acids are aggravated by the reduced conversion from the n-3 active products. This is due to the elevated intake of linoleic fatty acids and their competition for the conversion enzymes, namely, cyclooxygenase and lipoxygenase, at the cell membranes [35]. As a result, there is an overproduction of proinflammatory series 2 eicosanoid-like prostaglandins and series 4 leukotrienes compared with the noninflammatory series 3 prostaglandins and series 5 leukotrienes, which have anti-inflammatory, antiaggregatory, and vasodilatation properties [36–38].

Murakami et al [39] examined the associations between the dietary intake total n-3 polyunsaturated fatty acid and serum CRP concentrations and found an independent inverse association for both factors in a group of young Japanese women. Furthermore, considering the difficulties of consuming these nutrients through food and the uncertainties in terms of the absorption of α-linolenic fatty acid, many studies have been conducted to evaluate this fatty acid as a supplement and its impact on human health using different regimens and populations [40–42]. The effects on the prevention of atherosclerosis, chronic hepatitis, psoriasis, rheumatoid arthritis, myocardial infarction, asthma, and diabetes were described, and several studies demonstrated a decrease in proinflammatory cytokines [34–36,40,41]. Lopez-Garcia [43] observed a 29% decrease of serum CRP in a retrospective study that evaluated the uptake of αLNA through food in healthy women. Using short-term fish oil supplementation, Ciubotaru et al [44] found a 35% decrease of the CRP levels in postmenopausal women. In studies with healthy volunteers and patients with rheumatoid arthritis receiving FO and fish oil, control of inflammation was observed as reflected by a decrease in the mediators of the inflammatory process (cytokines, TNF-α, and IL-1β) [44].

Flaxseed oil does not contain EPA and DHA fatty acids but is rich in their precursor, αLNA. α-Linolenic acid is partially converted to longer chain n-3 polyunsaturated fatty acids, such as EPA (20:5n3) and DHA (22:6n-3); however, at present, it is not known what portion of αLNA undergoes these conversions in the plasma, cells, and tissues [45]. The hypothesis that the α-linolenic fatty acid present in FO is able to reduce inflammation in humans is supported by many studies. The effect of an FO-based diet on the synthesis of TNF-α and IL-1β was tested in healthy volunteers. Over a 4-week period, it was observed that its use inhibited the production of these inflammatory factors by approximately 30%, demonstrating its role as a potential inhibitor of these mediators [40]. Jenkins et al [19] suggested that the intake of grain flaxseed or FO decreases total cholesterol and HDL-c in humans. The effects of FO are mainly observed with regard to LDL cholesterol levels, with the levels of HDL-c and triglycerides being unchanged [46]. Lastly, Singer et al [47] reported a decrease in serum lipids with FO supplementation in patients with primary hyperlipidemia.

Surprisingly, there are few studies that have tested therapeutic interventions in the control of the inflammatory state in high-risk populations of uremic patients [14,42]. Considering the use of FO in other situations, the absence of significant side effects, the easy access and clinical applicability, the anti-inflammatory and antilipemic activity, and the beneficial effects observed in other situations on cardiovascular risk factors, we hypothesized that this agent could be useful in reducing the microinflammatory state in uremic subjects undergoing RRT with HD. In the present study, we observed that 4 months of FO supplementation appears to reduce the CRP levels in an early and sustained fashion. Interestingly, those patients who were previously inflamed seemed to have had better therapeutic results. Furthermore, a better response was observed in the lipid profile of the individuals supplemented with FO between the first and third periods of the study when compared with the placebo group. These data corroborate the studies conducted with n-3 fatty acids in their bioactive configuration (DHA and EPA) and may suggest that the amounts of αLNA converted into DHA and EPA are sufficient to obtain anti-inflammatory and antilipemic effects.

The limitations in the interpretation of this study are mainly due to the fact that the group of patients that received FO had higher CRP levels than the placebo group before the onset of the study, a situation that occurred because of a flawed randomization. Other limitations include the number of patients and the short-term duration of the study. However, as an exploratory study, we believe that these limitations do not invalidate the findings. Further supporting our results, we observed that the trend was significant in the patients who received the FO supplementation and did not occur in the placebo group by evaluating the changes in the inflammatory and noninflammatory state.

The results presented here support the hypothesis that FO and perhaps other anti-inflammatory therapies may have beneficial effects on the CRP levels in chronic HD patients. Our findings must be confirmed in different cohorts of uremic subjects. If the beneficial effect is confirmed, studies must be designed to optimize the doses and lengths of administration and to test the therapeutic efficiency on more relevant outcomes, such as cardiovascular and cerebrovascular events and mortality.

## Acknowledgment

This work was supported by the Research Incentive Fund from Hospital de Clínicas de Porto Alegre. The blinded capsules of placebo and FO were kindly provided by Naturallis Laboratories, São Paulo, Brazil. The authors disclose no conflict of interest.

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